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IN VITRO SUSCEPTIBILITY OF *BURKHOLDERIA* SPP. TO CATECHOL-SIDEROPHORE CONJUGATES WITH CEFACLOR

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Antibiotic therapy of infections caused by species of the genus *Burkholderia* is impaired by multiresistant strains partly due to low permeability of the outer membrane. Siderophores are excreted by bacteria to form conjugates with ferric ions which are reabsorbed by a protein transport system. Conjugates with β-lactams may serve as vehicles to cross the outer membrane. We analysed the in vitro activity of cefclor-catechol complexes against 42 *Burkholderia* strains from sputa of cystic fibrosis patients (*Burkholderia cepacia* [*B.ce.*] 24, *Burkholderia multivorans* [*B.mu.*] 9, *Burkholderia vietnamiensis* [*B.vi.*] 4, *Burkholderia gladioli* [*B.gl.*] 5). MICs were determined by an agar dilution technique with Iso-Sensitest Agar (Oxoid). The most active cefaclor-catechol complexes inhibited 50% of the strains of *B.ce.* GV I and IV, *B.mu.* and *B.vi.* at 0.13 µg/ml, of *B.ce.* GV III at 0.5 µg/ml and of *B.gl.* at 2 µg/ml. A concentration of 1 µg/ml inhibited all strains of *B.ce.* GV I and IV and of *B.vi.*, 78% of *B.mu.*, 56% of *B.ce.* GV III, and 20% of *B.gl.* strains. So subpopulations with high MICs exist among *B.mu.* and *B.ce.* GV III, while all strains of *B.gl.* included are less susceptible than those of other *Burkholderia* species. We conclude that in vitro activity of cefaclor-catechol complexes indicates a therapeutical potential for infections caused by *Burkholderia* spp. which merits further investigations.

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SUSCEPTIBILITY OF *STENOTROPHOMONAS MALTOPHILIA* TO MOXIFLOXACIN AND CIPROFLOXACIN ALONE AND IN COMBINATION WITH COLISTIN

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Stenotrophomonas maltophilia (*S.malt.*) has become a frequent pathogen in immuno-compromised hosts, e.g. cystic fibrosis patients. Therapy of infections caused by this pathogen is impaired by multiple antibiotic resistance. Fluoroquinolones (FQ) are among the options left for therapy and are frequently applied together with inhalative colistin (COL). We investigated the in vitro activities of the new FQ moxifloxacin (MOX) in comparison with ciprofloxacin (CIP) against *S.malt.* alone and in combination with COL. MICs were determined by a microtiter checkerboard procedure following NCCLS standards. 55 isolates of *S.malt.* from sputa of cystic fibrosis patients were included. MIC_{90}s (µg/ml) were: CIP 8, CIP in combination with COL 1, MOX 2, MOX in combination with COL 0.13. So by MIC_{90} MOX alone is 4 times more active than CIP alone, and MOX in combination with COL is 8 times more active than CIP in combination with COL. The percentage of strains inhibited by 0.25 µg/ml was: for CIP alone 14.6%, for CIP in combination with COL 65.5%, for MOX alone 23.6%, for MOX in combination with COL 98.2%. We conclude that MOX, particularly when it is combined with COL, presents a relevant progress for therapy of infections caused by *S.malt.* in cystic fibrosis patients.

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RISK FACTORS OF COLONIZATION AND/OR INFECTION BY STENOTROPHOMONAS MALTOPHILIA (SM) IN CYSTIC FIBROSIS PATIENTS

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Aims: To investigate potential risk factors of first-time Sm colonization or infection in CF patients. Methods: Multicentric (Lyon, Dijon) case-control study including 33 CF patients colonised by Sm and 60 age- and center-matched controls who have never been colonised by Sm. Results: Shwachmann and Brasfield score's means were lower in case than in control group (68.6 vs 80.6-p=0.001 and 16.7 vs 19.4-p=0.009). Predictive factors were: number of hospitalised days (4.5 days vs 1.4-p=0.008) and duration of oral antibiotherapy (50.7 days vs 22.4-p=0.008) in the preceding year. S. aureus was more frequently isolated in the sputum cultures of case patients preceding Sm colonization or infection (69.7% - n = 33 - vs 31.7% - n = 60 - p= 0.0001). Patients of the case group received more frequently antibiotics during the 30 days preceding sputum culture (54.5% vs 30%-p=0.01). This antibiotherapy more frequently included 3rd generation cephalosporins (36.4% vs 8.3%-p=0.001). A stepwise logistic regression model for Sm colonization was proposed with two variables: prior S. aureus colonization (OR=9.3–95%CI=2.3–38.6-p=0.002) and prior 3rd generation cephalosporin administration (OR=7.9–95%CI=1,7–36-p=0.007). Conclusion: The study confirms classical risk factor (3rd generation cephalosporins) but emphasizes the clinical relevance of prior S. aureus colonization as predisposing to Sm colonization or infection.

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STENOTROPHOMONAS MALTOPHILIA SURVIVES EXPOSURE TO CONCENTRATIONS OF TOBRAMYCIN USED IN AEROSOLIZED ANTIBIOTIC THERAPY

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The prevalence of respiratory tract colonization by *S. maltophilia* in patients with cystic fibrosis has increased in recent years. Precise reasons are unknown, although colonization has been associated with the use of broad-spectrum antimicrobial therapy. Isolation of *S. maltophilia* from home-use nebulizers has also been reported. We examined the ability of *S. maltophilia* strains from clinical (2) and environmental sources (2, plus a control strain) to survive exposure to clinically relevant (UK) concentrations (16,000mg/ml) of tobramycin and recorded their post-tobramycin exposure growth characteristics. All strains tested survived exposure to 16,000mg/ml of tobramycin. This was aided by the formation of biofilms which occurred with a variety of different media (nutrient broth, saline and tap water) on different surfaces (plastic and glass). Furthermore, recovery from plastic surfaces was significantly higher ($p \leq 0.05$) at 30°C and 20°C compared to 37°C. Organisms from biofilms formed in tap water were equally recoverable at all temperatures. Minimum inhibitory concentrations were recorded for each strain under all conditions, and these did not change pre- and post-tobramycin exposure. These findings suggest that *S. maltophilia* would be able to form and maintain viable biofilms on plastic nebulizer equipment used to deliver aerosolized tobramycin. The improved recovery of *S. maltophilia* at lower temperatures post-tobramycin exposure has implications for the analysis of samples of clinical and environmental origin when investigating the epidemiology of this organism in cystic fibrosis.

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CLINICAL SIGNIFICANCE OF ISOLATION AND TREATMENT OF ASPERGILLUS IN RESPIRATORY SECRETIONS OF CF PATIENTS

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Aspergillus fumigatus and other species are commonly isolated from respiratory secretions of CF patients with a prevalence reported of 10–57%. This organism may be associated with a pathological immune response (allergic bronchopulmonary aspergillosis), invasive disease, aspergillomas or no apparent pathology. The purpose of this study was to evaluate patients with Aspergillus as to their pulmonary function, hospital days and IV antibiotic days for the three years preceding and following their first positive culture. In addition, the positive Aspergillus group was further divided for comparison between those receiving treatment (corticosteroids and/or antifungal) and those not receiving such treatment. This was done by means of a retrospective review of 45 CF patients with positive sputum culture for A. fumigatus compared to a control group without Aspergillus matched for age, gender and pulmonary function prior to positive culture. A repeated measures analysis was used to follow the rate of decline in FVC and FEV1, days in hospital and days receiving IV antibiotics. There were no significant differences found between those with and without Aspergillus with regard to number of hospital days, days of IV antibiotics or rate of change of pulmonary function for the three years before and after positive culture. However, when examining only Aspergillus positive patients within the first year after positive culture, there was significantly greater improvement

of FVC in those treated versus untreated (P = 0.049). Patients with positive Aspergillus culture were more likely to have Pseudomonas aeruginosa and less likely to have Streptococcus Group A (P = 0.039 and 0.021, respectively). We conclude that the presence of Aspergillus is not necessarily associated with worsening in patient condition. However, in those who do appear to have lower pulmonary function associated with Aspergillus, treatment with antifungals and/or steroids appears helpful in returning them to baseline function. Treatment within the first year of positive culture may improve pulmonary function in selected patients.

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SEVERE BRONCHOMALACIA ASSOCIATED WITH BRONCHOPULMONARY ASPERGILLUS INFECTION IN CYSTIC FIBROSIS

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Allergic Bronchopulmonary Aspergillosis (ABPA) is a well-recognized complication of Cystic Fibrosis (CF). There are 3 published cases of fatal invasive bronchopulmonary disease due to Aspergillus fumigatus in CF patients, 2 of whom had been on systemic corticosteroids. We report our experience with severe bronchomalacia associated with aspergillus in 4 patients with CF (group 1), and compare them with clinic patients with ABPA (group 2), patients colonized with fungi without severe bronchomalacia (group 3), and patients who have no evidence of pulmonary fungal infection (group 4). The four patients were females 8–12 years of age. Three-quarters had received long-term treatment with nebulized tobramycin and had marked fluctuation in their pulmonary function. The other patient had progressive decline in pulmonary function associated with poor adherence to CF care. At bronchoscopy, all four patients had severe bronchomalacia and copious amounts of white or grey mucous. One patient also had considerable tracheomalacia. BAL cultures in all four patients grew heavy Aspergillus fumigatus and/or aspergillus species. None of these patients had immunologic evidence of ABPA. After failing treatment with oral itraconazole, three patients were treated with intravenous Amphotericin B and showed marked clinical and pulmonary function stabilization. The other patient stabilized spontaneously. Severe pulmonary function variability in these patients has persisted following therapy. Variability in FEV1, expressed as the standard deviation (SD) of FEV1 (% predicted), was 19% in group 1 and 19.6% in group 2 patients, which was significantly higher than in patients in groups 3 and 4, where it was 10.9 and 9% predicted, respectively ($p < 0.05$ by Tukey-B Multiple Range Test, 1-way ANOVA). The overall rate of decline was -9.5% predicted/year FEV1 in Group 1 patients, which was similar to group 2, 3, and 4 patients, where it was -8.4, -6.7, and -2.3% predicted/year, respectively ($p = 0.09$, ANOVA). We conclude that ABPA, and bronchopulmonary infection with aspergillus in CF in the absence of ABPA, is associated with marked variation in pulmonary function, and the latter may also be associated with severe bronchomalacia. Therapy with Amphotericin B may help stabilize lung function in this situation.

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INTERNALIZATION OF BEGIN LINE STAPHYLOCOCCUS AUREUS END LINE RN6390 BY CF AIRWAY EPITHELIAL CELLS IS DOSE- AND TIME-DEPENDENT AND INDUCES APOPTOSIS

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Begin Line Staphylococcus aureus End Line is the second most common pathogen isolated from the airways of cystic fibrosis (CF) patients. Often, in CF patients persistent Begin Line S. aureus End Line colonization of the respiratory system begins in early infancy followed by Begin Line Pseudomonas aeruginosa End Line infection. However, Begin Line S. aureus End Line colonization is also present in more advanced stages of the disease, co-infecting the airways with P. aeruginosa. Recently, persistent and relapsing infection with Begin Line S. aureus End Line has been linked to the ability of mammalian cells to internalize Begin Line S. aureus End Line, and in turn induce apoptosis. In this study, we examined internalization of Begin Line S. aureus End Line RN6390 and the ensuing induction of apoptosis in a CF airway epithelial cell line. Internalization of Begin Line S. aureus End Line revealed to be dose- and time-dependent and could be blocked by cytochalasin D. Results of internalization experiments indicated that replication of intracellular Begin Line S. aureus End Line was delayed with 3–4 bacterial divisions within 24 h. Transmission electron microscopy confirmed the intracellular location and replication of Begin Line S. aureus End Line within the cells and implied that Begin Line S. aureus End Line endocytosis occurred by a zipper-like mechanism. Apoptosis of epithelial cells induced by Begin Line S. aureus End Line required bacterial entry, and metabolically active cells and did not occur within the first 5 h after infection.

This work was in part funded by the Innovative Medical Research Fund of the University of Muenster, Germany. We thank Wilhelmina Hellmann for her assistance with transmission electron microscopy.

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RISING PREVALENCE OF NAFCILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (NRSA) AT A CF CENTER

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NRSA has been reported to occur infrequently in CF (<5%), although a recent report described a higher prevalence of staphylococcal aureus (SA) resistant to oxacillin (11.5%). Because of a perceived problem, we determined the prevalence of NRSA at our CF Center from 1993 - April 1999. Microbiology and medical records were reviewed for all CF patients followed during this time. Fifty-five percent (128/234) of the CF patients had at least sputum positive for SA. Of the 234 CF patients, 33 had NRSA (14%). The percent of SA resistant to nafcillin was 24.7% (33/128) compared to an overall hospital rate of NRSA of 20% in 1993 and 47% in 1998. Two-thirds of the CF patients with NRSA were > 18 years old. NRSA was present chronically in 26 of the 33 patients, whereas NRSA was transient in 7 patients. Fourteen of the 33 patients converted from nafcillin-sensitive SA to NRSA. The initial SA isolate identified in 12 patients was NRSA. Nine of the 33 patients underwent lung transplantation; 3 acquired NRSA post-transplant, 1 had NRSA only pre-transplant, and 5 patients had NRSA both pre- and post-transplant. There were no new cases of NRSA in 1993, 3 new cases in 1994, 1 new case in 1995, 8 new cases in 1996, 11 new cases in 1997, 7 new cases in 1998, and 3 new cases thus far in 1999. Thirty of the 33 patients were concomitantly colonized in respiratory tract with gram-negative aerobes. There is a higher prevalence of NRSA at our CF Center than previously reported in the literature, suggesting the potential for NRSA to become a more prevalent pathogen in CF. Most of our patients with NRSA were > 18 years old and are chronically colonized with this pathogen. Of the 6 lung transplant patients colonized with MRSA before transplantion, 5 continued to be colonized after transplantation.

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PRE-IMMUNIZATION ANTI-PNEUMOCOCCAL ANTIBODY TITERS ARE PROTECTIVE IN A MAJORITY OF CYSTIC FIBROSIS PATIENTS

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BACKGROUND: Although invasive pneumococcal disease is infrequent in CF, it is recommended that all CF patients receive pneumococcal immunization. As part of a comprehensive program to immunize our clinic population, we obtained pre-immunization anti-pneumococcal antibody titers. We hypothesized that the percentage of CF patients without protective levels of anti-pneumococcal antibody titers would be high, as they are exposed to frequent antibiotic therapy that would eradicate organisms prior to the generation of an antibody response.

METHODS: We prospectively obtained antibody titers to six pneumococcal serotypes as measured by ELISA in 101 unselected CF patients, aged 1–39 years, who had not previously been immunized. A protective level of antibody was defined as greater than 200 ng/ml. Fisher's exact test

was used to compare the proportions of protective antibody titers among patients with CF to those of normal controls obtained from the literature.

RESULTS: The percentage of CF patients with protective levels of antibody to serotypes 3 and 14 is given in the table. Reported levels of protective titers in healthy controls range from 28–53% and 16–67% for serotypes 3 and 14, respectively. Patients with CF are significantly more likely to have protective levels of antibody titers to these serotypes than healthy controls ($p < 0.01$).

CONCLUSIONS: In contradistinction to our hypothesis, CF patients are more likely to have protective pre-immunization anti-pneumococcal antibody titers than healthy controls. However, 17–24% of CF patients do not have protective antibody levels. Therefore, we concur with current recommendations for pneumococcal immunization.

Age (years)	n	Type 3	Type 14
all	101	83	76
1–9	36	72	61
10–19	28	82	82
20–29	22	100	82
30–39	15	87	93

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IMPROVED MOLECULAR DIAGNOSIS OF FUNGAL INFECTIONS IN PATIENTS WITH CYSTIC FIBROSIS

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Laboratory culture and serological methods continue to be the diagnostic cornerstone in the detection of medically important fungi infecting patients with cystic fibrosis. Of these, Aspergillus spp. and in particular A. fumigatus is responsible for a wide range of bronchopulmonary fungal disease, including allergics forms through to chronic necrotising aspergillosis. However, these organisms and the other filimentous fungi are difficult to culture in vivo conditions and therefore present diagnostic complications under such circumstances. Employment of the nuclear rDNA genes encoding the 5S, 18S, 5.8S and 28S rRNA offers a molecular basis for both the detection and the identification of fungi. The aim of this study was to (i). ascertain a suitable method to extract yeast/fungal DNA from sputum and BAL specimens from patients with cystic fibrosis, (ii). detect and identify these microbiological agents by amplification of various ribosomal target gene loci, i.e. small ribosomal subunit (18S rRNA), large ribosomal subunit (28S rRNA), 5.8S rRNA and interspacer regions ITS1 and ITS2, using PCR and direct sequence analysis, (iii). separate and identify multiple fungal agents in a single clinical specimen. Twenty-five medically important fungi, including Candida spp. [C. pseudotropicalis, C. kreusi, C. lusitaniae, C. guilliermondii, C. dubliniensis, C. parapsilosis, C. albicans, C. tropicalis, C. kefyr, C. (Torulopsis) glabrata,], Aspergillus spp. [A. flavus, A. terreus, A. fumigatus, A. niger, A. niduliaus], Fusarium spp. Paecilomycearomyces s spp., Cryptococcus neoformans, Chrysosporium spp., Acremonium spp., Scedosporium spp. Penicillium spp., Monolinia laxa, Alternaria alternata, and Saccharomyces cerevisiae were analysed by PCR amplification and sequence analysis in order to ascertain that the ITS region was the most suitable for detection and accurate identification.

This study demonstrated the optimal method of molecular detection and identification of fungi in sputa and BAL from CF patients included an initial DNA extraction method comprising treatment of the specimen with lyticase followed by extraction with proteinase K, guanidine hydrochloride. Primer selection indicated employment of the ITS1 and ITS 2 regions for detection and the 5.8S - ITS2 region for sequence identification. Where sputa are shown to contain several mixed fungal genera and species, it is recommended that each species is separated on a high-resolving acrylamide gel (ExcelGel 48S, Pharmacia), before excision and simple elution, reamplification and sequence analysis of single clones. In conclusion, this optimised method may allow for a better understanding of fungi in CF infection and help guide the most appropriate management of the patient, for example in lung transplantation.

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CYSTIC FIBROSIS RESPIRATORY SYNCYTIAL VIRUS (RSV) REGISTRY: YEAR 1 RESULTS

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Respiratory Syncytial Virus (RSV) infection prevalence and clinical impact in children with Cystic Fibrosis (CF) is not well described in the literature. An epidemiological registry was established during the 1996–1997 viral season to describe RSV infection and illness in children less than 2 years of age with CF. A total of 110 children were entered in the registry from 15 institutions between October 1, 1996 through May 30, 1997.

Data from 86 participants were analyzed, 9 incomplete data forms were excluded. One center provided complete data forms only for RSV positive hospitalizations from a cohort of children followed during the study. This cohort of 15 patients was included in the estimate of RSV hospitalization rate. Data collected included: demographics, medications, nature of clinic visit (symptomatic or asymptomatic), signs/symptoms at clinic presentation, hospitalization information, performance/results of RSV testing and serum lab tests.

Of those evaluable (n=86), 45% were female, 55% were male with a mean age of 12 months. Twenty-five of 86 (29%) enrollees required hospitalization at least once for respiratory illness, 8 children required multiple hospitalizations. Of 36 hospitalizations for respiratory illness, 12/36 (33%) were RSV related. A total of 30 RSV tests were performed with 13 RSV positive results (43%). Overall, 13/86 (15%) were RSV positive at time of presentation with respiratory symptoms. Twelve of 13 (92%) were hospitalized for RSV illness for a RSV hospitalization rate of 12/110 (11%). Of the 24 non-RSV related hospitalizations, RSV testing was not performed in 8 cases.

Of the 13 RSV positive cases, 69% were male, 31% were female with a mean age at presentation of 13 months. The most common presenting symptoms included cough (11), congestion/wheezing/rhinorrhea (each 7)and fever (8). Hospital admission was to the floor in 10/12 (83.3%) and to the ICU in 2/12 (16.7%). The mean duration of hospitalization was 12.3 days (147 total days, range 2 to 35 days).

Conclusion: Preliminary analysis of this Registry data suggests that RSV infection contributes substantially to respiratory illness in children less than 2 years of age with CF. Of those with virologically confirmed RSV infection, hospitalization was required in most cases and can be prolonged. RSV testing during the viral season was not routinely performed and therefore it is likely that the prevalence of RSV infection and illness has been underestimated. Effective measures to prevent RSV infection in infants with CF could reduce short-term, and potentially long-term, morbidity in these children.

PULMONARY

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HIGH RESOLUTION COMPUTED TOMOGRAPHY OF THE CHEST IN INFANTS WITH CYSTIC FIBROSIS

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High resolution computed tomography (HRCT) of the chest may be useful in detecting early disease-related changes in the lungs of infants with cystic fibrosis (CF). The purpose of this study was to survey the pathological abnormalities identifiable using HRCT imaging in infants with CF. Four 1 mm thick HRCT images were obtained at near full inflation (25 cm H_2O) and at end expiration (0 cm H_2O) during controlled pauses in ventilation on 32 infants with CF (mean age 121 weeks, range 10–285 weeks). Equivalent HRCT images were obtained on 14 infants without respiratory disease (mean age 99 weeks, range 20–232 weeks) who were undergoing HRCT for other clinical indications. Images were evaluated by a radiologist blinded to subject diagnoses using a modification of the CF HRCT scoring system described by Maffessanti et al. (J Thoracic Imaging 11:27–38,1996). Abnormalities were identified in 29 of the 32 infants with

CF and 4 of the 14 control (C) infants. Total HRCT severity scores for infants with CF and C infants were 13.8±12.6 and 0.6±1.3, respectively. Bronchiectasis, airway wall thickening, and parenchymal abnormalities were identified on the full inflation images of 31, 75, and 50%, respectively of the infants with CF and 0, 29 and 7% of the control infants. Gas trapping was present on the end-expiratory images in 69% of the infants with CF and 7% of the C infants. The abnormalities seen in the infants with CF were equally distributed in the right upper, right lower, left upper and left lower lung fields. Total severity and gas trapping scores were not significantly related to age. Pathological changes are present in the lungs of the majority of infants with CF. Airway wall thickening and gas trapping at end-expiration were the most frequently identified abnormalities. HRCT images of the chest obtained during controlled pauses in ventilation appear to be useful for identifying the earliest pathological changes occurring in the lungs of infants with CF.

(Supported by a grant from the CF Foundation.)

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UTILITY OF SPIROMETER-TRIGGERED HIGH RESOLUTION COMPUTED TOMOGRAPHY (HRCT) SCORES IN ASSESSING CHANGES IN CYSTIC FIBROSIS (CF) PATIENTS BEFORE AND AFTER TREATMENT FOR A PULMONARY EXACERBATION

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We investigated the utility of spirometer-triggered HRCT using a novel scoring system in 17 CF patients pre- and post-treatment of a pulmonary exacerbation. HRCT scores, PFTs, and clinical scores were evaluated to assess: (1) correlations between HRCT scores, clinical scores, and PFTs, (2) which components of the HRCT scores changed, and (3) which measures were most sensitive to change. **Methods:** Seventeen patients with mild – moderate CF lung disease (9F:8M, [mean ± SD] age: 18 ± 7 years, FEV_1: 63 ± 16 % pred., $FEF_{25–75\%}$: 37 ± 19 % pred.) with a pulmonary exacerbation were evaluated by spirometer-triggered electron beam CT scanning of the chest (1.5 mm collimation) at ≥ 95% SVC (inspiratory scans), and near FRC and RV (expiratory scans) at 6 anatomic levels of the lung, by PFTs, and by acute change clinical score (ACCS) before and at 15 ± 1 days after treatment. HRCT scans were independently reviewed by three radiologists. The scoring system incorporated "irreversible" (extent and severity of bronchiectasis and bronchial wall thickening) and "reversible" (mucus plugging, atelectasis/consolidation, and air trapping [AT]) components. Test sensitivity for different HRCT and PFT parameters were assessed by effect size analysis. **Results:** There was improvement in ACCS (17 ± 5 [$Test_1$], 9 ± 2 [$Test_2$], $p<0.01$), and selected PFTs (e.g. FVC 2.78 ± 0.80 L, $p<0.01$, FEV_1 1.96 ± 0.66 L [$Test_1$], 2.19 ± 0.73 L [$Test_2$], $p<0.01$, SVC 2.79 ± 0.82 L [$Test_1$], 3.07 ± 0.88 L [$Test_2$], $p<0.01$, and IC 2.11 ± 0.60 L [$Test_1$], 2.36 ± 0.64 L [$Test_2$], $p<0.05$), as well as a decrease in the total HRCT score (113 ± 16 [$Test_1$], 108 ± 16 [$Test_2$], $p<0.05$) and reversible component score (75 ± 11 [$Test_1$], 73 ± 10 [$Test_2$], $p<0.02$). Changes in total HRCT score and reversible component score correlated with change in FEV_1($r = -0.61$, $p < 0.02$, $r = -0.53$, $p = 0.03$). Change in FEV_1 correlated with change in ACCS ($r = 0.67$, $p < 0.02$). Effect size analysis showed a rank order as follows: reversible component score w/o AT 0.86 > reversible component score w/ AT 0.67 > total HRCT score 0.54 > FEV_1 0.37 > irreversible component score 0.32. **Conclusions:** Improvements occurred in total and reversible HRCT scores, in FEV_1 and other PFTs, and ACCS. Total and reversible HRCT scores were reproducible and more sensitive to change after treatment than conventional forced expiratory flow outcome measures.

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AEROSOLIZED RECOMBINANT HUMAN DNASE IN CYSTIC FIBROSIS PATIENTS YOUNGER THAN 5 YEARS OF AGE

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Objective: To evaluate the ability of high-resolution computerized tomography (HRCT) of the chest and chest radiography (CXR) to determine the effects of recombinant human DNase (rhDNase) in cystic fibrosis (CF) patients younger than five years of age. Design: Twelve patients with CF younger than five years of age at the University of Michigan Cystic Fibrosis Center were studied in a randomized, double-blind placebo-controlled study. Results: The difference in the mean changes of HRCT scores between the rhDNase and placebo groups was found to be significant at the 95% level (P=0.02). In subjects with higher initial HRCT scores, treatment with rhDNase improved the final scores, while those in the placebo group experienced a worsening of their scores. Analysis was done to relate specific HRCT changes (subscores) to total HRCT score. There was significant correlation between bronchiectasis, peribronchial thickening, mucus plugging, and air trapping and the total HRCT score (r=0.8, r=0.9, r=0.8, r=0.9 respectively, P<0.001 for all subscores). Acinar nodules/consolidation, thickening of intra-interlobular septae, and ground glass opacities were significantly correlated to the total HRCT score with P<0.05 with r=0.6 for all subscores. When the analysis was performed to relate the HRCT subscores to CXR score, only thickening of the intra-interlobular septae was significantly correlated with the total CXR score (r= -0.7,P<0.01). CXR scores showed improvement with rhDNase; however, the difference in the mean changes was not statistically significant (P=0.16). The administration of rhDNase reduced the rate of respiratory exacerbation requiring antibiotic therapy. There was improvement in the parents' assessments of the patients' well-being with improvement in physical activity, decreased cough, improved sleep quality and appetite with rhDNase. No significant adverse effects were noted. Conclusions: In CF patients < 5 years of age, the administration of rhDNase improved the HRCT scan (statistically significant) and CXR scores. It also reduced respiratory exacerbation and improved clinical status. Findings indicate that HRCT of the chest is useful and sensitive in studying response to therapy in patients with mild CF lung disease. Supported in part by NIH Grant #M01-RR000042, Genentech, Inc. and Dale Maxwell memorial funds.

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RECOMBINANT HUMAN DEOXYRIBONUCLEASE 1 INHALATION THERAPY IN CF PATIENTS IMPROVES LUNG FUNCTION BUT DOES NOT PREVENT PROGRESSION OF LUNG DESTRUCTION

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We began a two-year prospective open therapeutic trial with recombinant human deoxyribonuclease 1 (rhDNase) inhalation therapy in CF patients with normal lung function in 1997 to detect factors influencing the various benefits of such a therapy. In all, 39 CF patients took part in this study (25 male/14 female, mean age 12 years; range 6 - 18 years; FVC mean: 90.8 ± 11.3%, FEV_1 mean: 91.9 ± 14.2%). The study was completed with 36 CF patients. Regular lung function tests every three months and a HRCT-scan before and after two years under rhDNase therapy reflect the study protocol. We were able to support the known benefit of an early treatment of CF patients with rhDNase after the one-year analysis of this trial. However, we failed to demonstrate any correlation between the improvement of lung function tests and High Resolution Computer Tomography (HRCT) scores, in general, as well as the degree of lung destruction. The findings of the two-year analysis support the early (one-year) results. The HRCT controls showed unchanged Bhalla scores (1 point maximum difference) in 23 patients, whereas Bhalla scores increased in 13 patients (2 - 7 points) after two years, thus demonstrating ongoing lung destruction. Lung function increased after three months of rhDNase therapy (mean: 5.5% for FEV_1 and 5.5% for FVC). After one year of therapy, the results remained nearly unchanged. After two years of therapy, a further slight improvement of lung function could be demonstrated (mean: 7.2% for FEV_1 and 7.0% for FVC). The improvement of lung function was similar in patients with un-

changed as well as increased Bhalla scores. Patients colonized with Pseudomonas aeruginosa as well as non-colonized patients presented similar increases in FEV_1 values, whereas a rather impressive higher increase of FVC values was shown in colonized patients in contrast to non-colonized patients (10.5% and 3.9%, respectively). A slight reduction of the rate of infections calculated on the basis of one-year intervals was observed under rhDNase therapy in comparison to the pretreatment period (minus 12 - 0 months: 63; 0 - 12 months: 54; 12 - 24 months: 43 infections).

In conclusion, the presented data support the benefit of early rhDNase therapy, even in patients with normal lung function. Patients colonized with Pseudomonas aeruginosa may profit more in terms of better FVC values. However, improvement of lung function does not prevent ongoing lung destruction in some patients.

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CAN WE ACCURATELY MEASURE LUNG DEPOSITION OF INHALED ANTIBIOTICS?

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The effective administration of therapeutic agents by nebulization generally requires the agent to have a high safety index since pulmonary deposition is variable and highly unpredictable. Future CF drugs may not offer such tolerance to dosage, and thus accurate predictions of pulmonary deposition will be essential. Historically, nuclear medicine deposition studies have been associated with problems surrounding variations in pre- and post-nebulization geometry, tissue attenuation, and loss of radiation during nebulization. The purpose of this study was to develop an accurate technique for measuring pulmonary deposition of tobramycin and to confirm the precision by accounting for all radioactivity pre- and post-nebulization. The anterior-posterior tissue attenuation factors of 10 healthy adults were measured using a cobalt flood source (J Nuc Med 23:731,1982). A 4 mL solution of 80 mg tobramycin with 8 mCi ^{99m}Tc labeled human serum albumin was nebulized using the Pari LC Star nebulizer driven by a PulmoAide compressor. There was a filter on the expiratory limb of the circuit. The radioactivity in the nebulizer was quantified pre-nebulization. Post-administration the subject swallowed water to clear the upper airway of radioactivity. Using "regions of interest," the radioactivity was quantified in the lungs, esophagus and trachea, and stomach of each subject taking into account each individual's attenuation factor. The activity remaining in the entire apparatus was also measured. An accuracy of 99±2 % was attained between the pre- and total post-nebulization counts. There was also agreement between the conventional quantification of nebulizer drug output and that calculated using the counts of radioactivity. The rates of pulmonary and total body deposition were 1.30±0.16 and 2.10±0.19 mg/min, respectively. Total expected deposition was determined to be 11±1.1 mg. The in vivo respirable fraction was 0.62±0.07 which agreed with previous in vitro work (Chest 113:951,1998). In conclusion, this technique uses pre- and post-nebulization comparisons of radiation to demonstrate the accuracy of measurements of pulmonary and extrapulmonary deposition of inhaled tobramycin aerosol and would be suitable for quantifying the deposition of any other nebulized therapeutic agent.

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BRONCHODILATOR RESPONSIVENESS IN INFANTS WITH CYSTIC FIBROSIS

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Bronchodilator responsiveness is common in older children and adults with cystic fibrosis (CF). The purpose of this study was to compare airway responsiveness to albuterol in infants with CF to that of normal infants. Infants were sedated with chloral hydrate (75–100mg/kg). Maximal expiratory flow-volume curves (MEFVCs) were obtained at baseline as described by Feher et al (J Appl Physiol 1996, 80:2019–2025). Albuterol was then given using a metered dose inhaler with a spacer (Aerochamber MV, Monaghan Medical Corp.) in a dose of 2 puffs (180µg). Each puff was followed by an inflation of the lungs to 25 cm H_20. Adequate systemic drug delivery was assumed when a 10% increase in heart rate was achieved. A second dose of 2 puffs was given if a 10% increase was not achieved at 2 minutes after the first dose. MEFVC maneuvers were repeated 10 minutes following the first dose of albuterol. Mean values of the 3 best pre- and post-albuterol maneuvers were used for analysis. Thirteen pre- and post-albuterol measurements were made on infants with CF (ages 48–191 weeks). Twenty-eight pre- and post-albuterol and 13 placebo measurements were made on normal healthy infants (ages 6–141 weeks). Eight of 13 infants with CF (62%) and 6 of 28 normal infants (21%) responded to albuterol with percent increase in FEF_{75} greater than 2 standard deviations from the mean change in FEF_{75} seen in the placebo group. FVC, $FEF_{25–75}$, FEF_{75}, and FEF_{85} changed by a mean of 5, 9, 19, and 22%, respectively, in infants with CF. This differed significantly from the normal infants who received albuterol who demonstrated mean changes in FVC, $FEF_{25–75}$, FEF_{75}, and FEF_{85} of 0.4, 2, 5, and 6%, respectively ($p<0.025$). The changes in the CF group also differed significantly from the placebo group. Percent changes in FEF_{75} and $FEF_{25–75}$ following albuterol declined significantly with age in the normal patients, but not in the infants with CF. Infants with CF demonstrate more frequent bronchodilator responsiveness to albuterol than normal infants. This response is also of greater magnitude than that seen in normal infants.

Supported by: NIH HL54062.

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LUNG FUNCTION CHANGES IN RELATION TO MENSTRUAL CYCLE IN FEMALES WITH CYSTIC FIBROSIS

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Background - Women with cystic fibrosis (CF) have reported worsened lung symptoms in association with menstruation. Estrogen and progesterone have been shown to have impact on CF gene expression, tone of smooth muscle in the airways, immune response and cytology in the tracheobronchial epithelium. We wanted to study the influence of menstrual cyclicity on airway symptoms among CF females. Methods - Twelve CF women (mean age 30 years, mean Shwachman score 85) kept daily records during three menstrual cycles on lung function, sputum quality and need for intravenous antibiotics. Paired t-test was used as statistical method to compare the airway symptoms between the luteal phase and menstruation. Results - FEV1 was significantly higher during the luteal phase compared to during menstruation (mean 66% vs. 61%, p=0.003). FVC showed the same pattern being significantly higher during the luteal phase compared to during menstruation (mean 75% vs. 70%, p<0.001). There were no statistical differences in sputum quality or in the use of intravenous antibiotics when comparing the two time periods. Conclusion - Lung function changes were found during menstrual cycles in women with cystic fibrosis. It is probably related to hormonal changes during menstrual cycles. Previous studies have shown that progesterone may relax the tone of the smooth muscle in the airways. These results warrant further studies to understand the complexity of CF lung disease in women.

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INVOLVEMENT OF MMPs/TIMPs BALANCE IN CYSTIC FIBROSIS: POTENTIAL ROLE OF GTP-DEPENDENT SIGNAL TRANSDUCTION PATHWAYS

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Pulmonary tissue damage in Cystic Fibrosis (CF) is mainly due to the release of proteases by neutrophils. The role of matrix metalloproteinases (MMPs) and their inibitors (TIMPs) is not still clearly defined.

Objectives: 1) to evaluate the contribution of the different MMPs isoforms to total gelatinolytic activity respect to the inhibitory potential of TIMP-1/-2 (inhibitors of type IV collagenases) in bronchial secretions (BS) and bronchoalveolar lavage fluid (BAL) of patients with CF; 2) to study the effect of LPS on MMPs activity and inibition in short-term cultures of BAL cells; 3) to study in HL-60 cell line, the effects of GTP depletion on leukocytes differentiation and other cellular functions. Methods: we collected 11

BS from CF pts and 14 BAL (4 CF pts, 10 Chronic Lung Disease pts); zymograms and reverse-zymograms were performed on fluid phases (FP) of centrifuged specimens and on conditioned media (CM) of short-term cultures of BAL cells. We performed: evaluation of PG-E2 levels on CM of short-term cultures (RIA); treatment of HL-60 cells with mycophenolic acid (MPA) and guanosine that reverse MPA effects by increasing GTP pool; evaluation of cell differentiation by FACS analysis of CD11b and generation of superoxyde; cellular proliferation by BrdU incorporation (ELISA), GTP levels by HPLC. Results: 1) in the Fps of all BS and BAL both type IV collagenases are present; TIMPs are present mainly as complex (12/13 BS) and, as single bands of 28 and 21 kD, on 4/11 BS and 1/2 BAL vs 4/4 positive control samples (28 kD form); 2) in short-term cultures of BAL cells LPS increases the production and the activity of both type IV collagenases (92 and 72 kD) with an increase of PG-E2 level in CM; in BS and CM of short-term cultures, the activation of the 72 kD isoform was evident in CF but not in control; 3) in HL-60 cells MPA induces a time and dose-dependent inhibition of proliferation and decrease on GTP pool, while low MPA level was associated with an increase of both differentiation indexes.

Conclusions: the imbalance MMPs (type IV collagenases)/TIMPs may play an important role in lung tissue damage in CF.

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ASSESSMENT OF AEROBIC FITNESS USING THE GAS EXCHANGE THRESHOLD IN CYSTIC FIBROSIS PATIENTS WITH MILD, MODERATE AND SEVERE LUNG DISEASE

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Higher levels of aerobic fitness are associated with increased longevity in cystic fibrosis (CF) (Nixon et al., NEJM, 1785, (327), 1992). The gas exchange threshold (GET) is a non-invasive means of detecting the lactate threshold (LT) which may be suitable for repeated fitness assessment in patients with CF. However, the characteristic abnormalities of ventilation and gas exchange seen in CF, by impairing CO_2 excretion, may preclude its use in patients with a significant reduction in lung function. This study was undertaken to determine if the LT could be identified non-invasively in CF patients, in particular, those with more severe lung disease. Twenty-eight patients (FEV_1 23–114% pred.) who were recruited from the adult CF clinic at St Vincent's Hospital, gave written informed consent and undertook a progressive exercise test on a cycle ergometer to exhaustion. Breath-by-breath gas exchange was measured using a Sensor Medics Vmax229 metabolic cart. Arterialised-venous blood was sampled for the purpose of LT determination by the log-log technique (Beaver et al., JAP, 2020, (60), 1986). The GET was determined using the modified VSlope method. Agreement between the thresholds was assessed using the technique of Bland and Altman (Lancet, 307, (I), 1986). An LT could not be determined in two subjects and they were excluded. A further two subjects were excluded because their GET occurred within the first two minutes of the exercise ramp and their GETs may represent "pseudo thresholds." The mean difference for the 24 subjects (LT-GET) was -10 $ml \sum min^{-1}$, not significantly different from zero and the limits of agreement were ± 410 $ml \sum min^{-1}$. Furthermore, the agreement of the GET with the LT was similar in those subjects with mild (FEV_1 > 70 % pred.), moderate (FEV_1 40–70 % pred.) and severe lung disease (FEV_1 < 40 % pred.). These findings indicate that the non-invasive GET may be used to estimate the LT in patients with CF of widely varying lung function, in contrast to the failure of this technique in adults with more severe obstructive pulmonary diseases of other aetiologies.

Supported by Cystic Fibrosis Association (Ireland) and Health Research Board (Ireland).

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CORRELATION BETWEEN DIGITAL CLUBBING AND PULMONARY FUNCTION IN CF PATIENTS

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Does the degree of digital clubbing reflect the severity of pulmonary function abnormalities in CF patients? The significant correlation between digital clubbing and certain pulmonary function derangements (hypoxemia and FEV1) is described. However, the relationship between digital clubbing and other parameters of pulmonary function is unclear. To determine if there is a relationship between digital clubbing and these other pulmonary function measurements in CF patients, we compared digital clubbing index (CI) to age, gender, and pulmonary function tests in CF patients. The CI of patients with CF was compared to age and gender-matched healthy controls. Data collected included demographics, CI (measured as the ratio of distal phalangeal depth to interphalangeal depth), total lung capacity (TLC), residual volume (RV), forced expiratory flow (FEV1), mean maximal expiratory flow (FEF25–75%), arterial oxygen tension (PaO2) on room air, and arterial carbon dioxide tension (PaCO2). Digital clubbing was defined as a CI 1. Pulmonary function data were compared to CI using Pearson bivariate correlation analysis (2-tailed). Comparison of digital clubbing in CF patients versus controls was by Fisher's Exact Test. Significance was set at $p < 0.05$. There were 58 CF patients (26 males:32 females; mean age 16.5 ± 7.6 yrs) and 58 age and gender-matched normal controls. 33/58 CF patients (58.9%) had digital clubbing versus 0/58 controls ($p = 0.001$). In CF patients, CI was positively correlated with RV ($p = 0.04$; Pearson 0.256) and was inversely correlated with PaO2 ($p = 0.001$; Pearson -0.404), FEV1 ($p = 0.0001$; Pearson -0.593), and FEF25–75% ($p = 0.0001$; Pearson -0.430). There was no significant correlation between CI and age ($p = 0.97$; Pearson -0.005; ns); TLC ($p = 0.24$; Pearson -0.151; ns); or PaCO2 ($p = 0.10$; Pearson 0.206; ns). We conclude that the degree of digital clubbing in CF patients is related to the degree of hypoxemia, airways obstruction (small, medium, and large airways), and hyperinflation.

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RESPIRATORY MUSCLE STRENGTH INCREASES DURING ACUTE HOSPITALIZATION IN CYSTIC FIBROSIS PATIENTS

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Does respiratory muscle strength (RMS) improve in CF patients? Is there any association between changes in RMS and changes in pulmonary function tests (PFT) or in anthropomorphic measures of nutrition? To answer these questions, we measured maximal expiratory pressures (MEP), maximal inspiratory pressures referenced to residual volume (MIP-RV) and FRC (MIP-FRC), PFT, body weight, midarm circumference, and triceps skinfolds biweekly in 14 consecutive CF children (6 males: 8 females; mean age 15.9 ± 4.4 years; range 7.8 - 21.2 years) during acute, non-ICU hospitalization at Childrens Hospital Los Angeles. Data were analyzed using Student's t-test and bivariate Pearson correlational analysis (2-tailed). The average length of hospitalization was 14.9 ± 5.0 days. During hospitalization, there was a significant increase in MEP (35.2 ± 20.0 cmH2O; $p < 0.001$), MIP-RV (21.3 ± 16.7 cmH2O; $p < 0.001$), and MIP-FRC (26.8 ± 15.1 cmH2O; $p < 0.001$). Overall, patients had a mean increase in vital capacity (11.8 ± 13.1%; $p = 0.005$), decrease in RV (45.5 ± 54.7%; $p = 0.008$), increase in FEV1 (10.3 ± 9.1%; $p < 0.001$), increase in weight (1.1 ± 1.7 kg; $p = 0.04$); increase in midarm circumference (0.5 ± 0.5 cm; $p = 0.001$); and an increase in triceps skinfold (0.2 ± 0.2 cm; $p = 0.006$). There was no significant change in oxygen saturation (1.2 ± 2.3%; $p = 0.07$, ns). MIP-RV was positively correlated with FEV1 ($p = 0.04$; Pearson 0.463), weight ($p = 0.035$; Pearson 0.473), and midarm circumference ($p = 0.041$; Pearson 0.460). Weight was positively correlated with midarm circumference ($p = 0.002$; Pearson 0.647) and triceps skinfold ($p = 0.041$; Pearson 0.461). There was no correlation between MEP and MIP-FRC with changes in VC (MEP $p = 0.06$, ns; MIP-FRC $p = 0.96$, ns), RV (MEP $p = 0.38$, ns; MIP-FRC $p = 0.70$, ns), or oxygen saturation (MEP $p = 0.94$, ns; MIP-FRC $p = 0.47$, ns). We conclude that respiratory muscle strength improves after treatment of pulmonary exacerba-

tions in our hospitalized CF patients. These improvements cannot be explained solely by changes in respiratory mechanics and improvement in measures of pulmonary function. We speculate that nutrition may play a significant role in respiratory muscle strength recovery.

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ROLE OF PULMONARY FUNCTION AND CARDIOPULMONARY EXERCISE TESTING IN PREDICTING WORK IMPAIRMENT/DISABILITY IN CYSTIC FIBROSIS

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With increasing numbers of adult CF patients in the workplace, clinicians are being called upon to evaluate disease-related disability. We examined relationships between pulmonary function and work/school capability and determined whether quantitation of aerobic fitness improved predictability of impairment/disability. The 131 adult patients attending our CF clinic were grouped according to their work/school status and the American Thoracic Society impairment/disability criteria (i.e., normal or mildly impaired: % predFEV1 ≥ 60% predicted; moderately impaired: %predFEV1 = 41 to 59% predicted; severely impaired: %predFEV1 values ≤ 40% predicted) into:

1.Work or attend school full-time: classified as normal or mildly impaired (N=30), moderately impaired (N=18) and severely impaired (N=28).

2.Work or attend school part-time: classified as normal or mildly impaired (N=10), moderately impaired (N=7) and severely impaired (N=9).

3.Are unemployed due to poor health and are classified as normal or mildly impaired (N=7), moderately impaired (N=3) and severely impaired (N=6).

A representative subgroup was studied with lung function and cardiopulmonary exercise tests, work/education questionnaire completed and clinical scores obtained. Subjects were further classified into the following 3 groups based on their questionnaire responses: G1: employed or attending school and did not miss work in the past year due to CF (N=33); G2: employed or attending school and did miss work in the past year due to CF (N=25); G3: unemployed due to CF (N=11). In single variable analysis current FEV1, VO2max, change in FEV1 over 2 years (i.e., ΔFEV1 = FEV1(1996)-FEV1(1998)/FEV1(1998)) and Schwachman-Kulczycki (S-K) clinical scores were associated with disability.

Ordered logistic regression analysis with multiple variables showed only current FEV1 was independently predictive of disability. We conclude that after accounting for current level of FEV1, other physiological measures are not additive in predicting disability for CF adults. Additionally, threshold values for FEV1 used to predict disability in other chronic respiratory disorders have limited discrimination for CF patients.

	G1	G2	G3
Age (yrs.)	27.5 (7.5)	31.0 (7.7)	33.5 (11.2)
%predFEV1 (%)	62.5 (23.7)	44.2 (18.5)	43.7 (19.9)
ΔFEV1 (L)	0.12 (0.39)	0.19 (0.21)	0.05 (0.17)
S-K clinical scores	73.3 (14.2)	61.6 (17.4)	58.6 (18.7)
Brasfield scores	15.5 (3.7)	13.3 (4.3)	13.9 (3.5)
Resting SpO2 (%)	96.4 (1.5)	95.8 (2.2)	96.0 (2.1)
SpO2(start-max) (%)	3.2 (3.1)	4.0 (3.4)	4.7 (4.4)
%predVO2max	79.3 (14.1)	77.6 (24.9)	66.0 (19.8)

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KNOWLEDGE AND USE OF INHALER THERAPY IN ADULT CYSTIC FIBROSIS

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Inhaler therapy is an important part of the overall management of pulmonary disease in cystic fibrosis (CF), but no specific guidelines have been developed for inhaler use in CF. The aim of this survey was to investigate current use and knowledge of inhalers among adult patients with CF. All patients at our adult CF centre (n=76) were invited to complete a questionnaire on their current inhaler therapy. Questionnaires were returned from 81% (62/76) of patients, of which 68% (42/62) currently used inhalers as part of their daily regime. For all patients recent spirometric measures of lung function (FEV_1% predicted) were obtained from their medical notes. The majority of patients (88%, 37/42) routinely used short acting bronchodilators. Less patients used inhaled corticosteriods (71%, 30/42) or long acting bronchodilators (64%, 27/42). In patients with severe disease (FEV_1 <30% predicted), 2/4 used short-acting bronchodilators. All patients in this group used inhaled steroids and long-acting bronchodilators. For patients with moderate disease (FEV_1 =30–70% predicted), 20/22 used short-acting bronchodilators, 17/22 used inhaled steroids and 14/22 used long-acting bronchodilators. For patients with mild disease (FEV_1>70% predicted), 15/16 used short-acting bronchodilators and 9/16 used inhaled steroids and long-acting bronchodilators. Most patients were aware of the reasons for using short- and long-acting bronchodilators and inhaled corticosteriods. Seventeen percent (5/30) reported that there was no clear benefit from using inhaled steriods. Over half of the patients (63%, 19/30) were aware that oral thrush was a potential side-effect of inhaled steriod therapy and took the appropriate precautions. Although there are no national published guidelines regarding the correct order of administration of inhaled therapies, local guidelines have been developed within the adult CF unit, but over half of the patients did not adhere to these guidelines. The assessment of inhaler technique forms an important part of the routine physiotherapy assessment, yet only 55% (23/42) of patients were aware that this was part of the physiotherapists repertoire, and 38% (16/42) reported that their inhaler technique had not been formally assessed by any member of the CF multidisciplinary team. 81% (34/42) of patients reported they were satisfied with their knowledge of inhaler therapy. In view of these findings there is need for further research to delineate the role of inhaled therapy in the management of pulmonary disease and to facilitate the development of clear guidelines regarding the use of inhaler therapy in CF.

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USE OF BRONCHOSCOPY TO DIRECT THERAPY IN INFANTS AND YOUNG CHILDREN WITH CYSTIC FIBROSIS

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Infants with cystic fibrosis frequently present with persistent cough and/or wheezing, but the specific etiology of these symptoms is often unclear. At our center we practice an aggressive approach to define presence and severity of infection in symptomatic patients. Infants and children with persistent respiratory problems who are unable to produce sputum undergo bronchoscopy to obtain lower airway secretions. If indicated by the history or by macroscopic appearance of airway secretions a central intravenous line is placed while the patient is sedated for bronchoscopy. Initial antimicrobial treatment is based on previous cultures and gram-stain and modified when bronchoalveolar lavages (BAL) cultures and sensitivities are available. Infants with negative BAL cultures are evaluated for other causes of cough/wheezing (gastroesophageal reflux, reactive airway disease). Here we present data collected over five years for all CF patients younger than 5 years of age who underwent bronchoscopy. Between 1/94 and 12/98 150 BALs were performed on 80 CF patients. Multiple procedures were performed in 36 patients: Two in 18 patients, 3 in 10 patients, 4 in 4 patients, 5 in one patient and 7 in 3 patients. 45/150 BAL cultures yielded no significant bacterial infection (<50,000 cfu/ml) or viruses. The 105 positive BAL cultures grew the following organisms either alone or in combination: S. aureus 36, P. aeruginosa 32, H. influenzae 29, S. maltophilia 11, S. pneumoniae 9, other bacteria in 7 specimens. MAI was recovered in 2 patients and viruses in 11 patients. A deep pharyngeal culture within one month prior to bronchoscopy was obtained on 42 occasions. BAL culture yielded a different result in 23/42(52%). Selection of therapy based on only upper airway cultures would have resulted in unecessary treatment in 9/23 and inadequate therapy in 16/23.

We conclude that the bronchoscopic approach is beneficial to determine specific infectious or non-infectious causes for continued respiratory symptoms. This approach can prevent both unnecessary antibiotic treatment and delayed intravenous antibiotics for infants with P. aeruginosa. To evaluate long-term effects of this strategy we are tracking lung function and resistance patterns in patients who had this aggressive approach during early childhood.

M. Muhlebach is supported by the CFF Clinical Fellowship grant.

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DIFFERENCES IN BAL NEUTROPHILS BETWEEN CF PATIENTS HOMOZYGEOUS AND COMPOUND HETEROZYGEOUS FOR DF 508

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Cystic fibrosis is associated with a neutrophil dominated airway inflammation which is detectable by bronchoalveolar lavage (BAL) early in the course of the disease. To assess whether different genotypes are associated with differences in the neutrophilic airway response, we have studied 96 stable CF patients aged 5 to 37 years with a mean FEV1 of 96 (15) % (SD). BAL was performed as a baseline investigation for the BEAT (BAL in the Evaluation of Anti-inflammatory Treatment) project in the lingula or one of its segments with 3 ml/kg body weight normal saline. The first recovered aliquot was treated separately; subsequent samples were pooled for analysis. BAL differential cytology was obtained after centrifugation at 500g for 10 minutes from smears stained with May-Gruenwald-Giemsa. Genetic analysis was performed for the 10 most prevalent CFTR mutation in Germany. 66 patients were homozygeous and 19 compound heterozygeous for the DF508 mutation; other less frequent genotypes were not included in this analysis. Patients homozygeous for the DF508 mutation had a significantly higher percentage of BAL neutrophils in pooled BAL samples compared to patients heterozygeous for DF508 ($p<0.01$, Wilcoxon test). No differences were observed between the 2 groups in lung function, bacteria in BAL fluid or percentage of patients colonized with P. aeruginosa. Therefore, neutrophil dominated airway inflammation was more pronounced in patients homozygeous for DF508 compared to those heterozygeous for this mutation. Whether this difference persists over time and is associated with a different clinical course will be answered when follow-up data are available for these patients.

Supported by Mukoviszidose e.V. and Roche, Germany.

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OPTIMIZATION OF SPUTUM PROCESSING TECHNIQUES FOR AIRWAY INFLAMMATION ASSESSMENT IN CYSTIC FIBROSIS

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Airway inflammation, the major cause of lung destruction in cystic fibrosis (CF) patients, is characterised by a persistent influx of neutrophils. Sputum analysis is considered as a non-invasive method to investigate airway inflammation. However, the applicability of the processing methods used in asthma to CF sputum is not known, as the viscoelasticity of both sputums is different. The aim of this study was to optimize CF sputum techniques suitable for both cell analysis and inflammatory markers detection. Fifteen sputums obtained from severely ill CF patients (n = 9, mean age = 22.5 years, 19% > FEV1 < 60%) were split into 5 equal plugs and dispersed either with PBS, DTT (0.1%), Dnase (10 UI/ml), a mixture of Dnase-DTT or 100µM Nacystelyn (a new thiol-containing mucoactive drug in clinical development) . We looked at cell viability, total cells and neutrophil counts. Total cell counts were determined using an haemocytometer and compared to the counts obtained in an automated hematology analyser. IL-8 level and HNE activity were assessed in sputum supernatant. Significant correlation was found between the manual and automated total cell counting for each cell dispersal method (r range, 0.7 and 0.9, $p<0.05$) showing the equivalence of both methods of cell counting. Mean cell viability (range, 71% and 76%), mean total cell count (range 18.4 and 26.6 x 10^3 cells/µl), mean neutrophils count (range 17.4 and 25.1 x 10^3 /µl), and mean supernatant IL-8 level (range, 7.6 and 11.3 ng/ml) were not significantly different between each cell dispersal method. However, free active elastase levels were significantly higher when sputum is processed using DNase suggesting the release of cell/DNA bound elastase. The concentration of IL-8 correlated with neutrophils counts with each sputum treatment (mean $r = 0.7$, $p< 0.05$). In Dnase-DTT processed sputum, negative correlation ($r = -0.6$, $p < 0.01$) was found between elastase activity and pulmonary function tests (FEV_1,FVC and R_{aw}). Neutrophils count also negatively correlated with FEV_1 ($r = -0.5$, $p = 0.05$) and FVC ($r = -0.6$, $p = 0.02$). These preliminary results demonstrate that sputum analysis involving an automated cell count is a useful method to assess airway inflammation in CF. The method could therefore be applied for CF clinical trials assessing the effect of any anti-inflammatory therapy.

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REGIONAL MUCOCILIARY CLEARANCE IN PATIENTS WITH CYSTIC FIBROSIS

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AIM: To perform a retrospective analysis of mucociliary clearance (MCC) studies in a large cohort of cystic fibrosis (CF) patients and age-matched healthy subjects. METHODS: Fifty-nine CF patients were studied on a total of 184 occasions, while 17 normal subjects were studied a total of 22 times. Patients were categorized as having either mild, moderate or severe disease according to their lung function. MCC was measured for 60 minutes from the whole, central, intermediate, peripheral, basal, mid and apical regions of the right lung using a radioaerosol and gamma camera technique following controlled deposition of the radioaerosol. Attempts were made to identify factors that may influence MCC in both normal subjects and CF patients using a stepwise multiple regression model. RESULTS: Compared with normal subjects, clearance in the CF patients was impaired in the whole right lung (28.0±3.7% vs 14.2±1.4%, p=0.0001) and in the central (35.6±4.3% vs 19.1±1.9%, p=0.0002), intermediate (25.5±3.7% vs 10.7±1.6%, p=0.0001), apical (31.6±4.6% vs 12.4±2.6%, p=0.002) and mid (30.4±4.0% vs 14.0±1.9%, p=0.0002) regions of the lung. MCC also tended to be slower in the CF patients in the peripheral (12.1±3.6% vs 9.2±1.9%) and basal (19.3±3.6% vs 14.5±1.8%) regions of the lung; however, it did not reach significance. There was a significant difference in clearance between the normal subjects and each of the individual patient groups (mild, moderate, severe) for whole lung, central, intermediate, mid and apical regions (p=0.002). However, there were no differences between the CF patient groups. Age, gender, body mass index, patient genotype (F508/F508 vs F508/X vs X/X), penetration index, number of recorded coughs and various lung function parameters were not found to significantly influence MCC using a predictive model. There was no difference in clearance between repeat study days for both the normal subjects (25.8±8.8% vs 20.4±3.3%, n=5, p=0.4) and CF patients (14.5±1.7% vs 14.4±1.7%, n=46, p=0.9) studied on two occasions. CONCLUSION: MCC is impaired in whole lung as well as most of the defined regions in CF patients compared with normal subjects. The impairment was present in all groups of CF patients, regardless of lung function, and values appear to be approximately 50% of those for normal subjects. Even the patients with preserved lung function (FEV1>80% predicted) had impaired clearance. Using a controlled breathing pattern, the measurement of MCC appears to be repeatable within subjects for both the normals and CF patients.

Supported by National Health and Medical Research Council and the Australian Lung Foundation.

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ASSESSMENT OF NON-INVASIVE MARKERS OF INFLAMMATION IN CYSTIC FIBROSIS

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Non-invasive assessment of pulmonary inflammation may provide a useful end-point for CF therapeutic studies. We have investigated the use of breath condensate (BC) to measure markers of inflammation including nitrate/nitrite together (NO_2^-+NO_3^-), nitrite alone (NO_2^-) and the inflammatory cytokine interleukin 8 (IL-8) and exhaled gas to measure carbon monoxide (CO). Increased levels of NO_2^-, a stable end-product of nitric oxide (NO) metabolism, has been demonstrated in the BC of subjects with CF despite evidence that exhaled NO itself is not elevated, even during res-

piratory exacerbations. We have studied whether concomitant analysis of NO_3^-, a second metabolite of NO, offers any increase in assay sensitivity for the assessment of mild lung disease. BC was collected in 11 clinically stable patients with $FEV_1 \geq 70\%$. Compared to age-matched, non-CF control subjects (n=9) where $NO_2^-+NO_3^-$ was 0.43 ± 0.29 μM, levels were significantly higher in CF subjects (6.05 ± 0.79 μM, $p<0.01$). NO_2^- alone (4.63 ± 0.92 μM), when assayed separately, represented $76 \pm 6\%$ of the combined total. Thus, analysis of nitrate and nitrite does not seem to provide any significant advantage over nitrite alone. BC from subjects with an acute respiratory exacerbation (n=8) was also used to measure IL-8, known to be elevated in CF sputum. No IL-8 was demonstrable by ELISA in any of the patients studied. Finally, exhaled carbon monoxide generated in the presence of haem oxygenase, a component of macrophages and other inflammatory cells, has previously been shown to be elevated in asthmatic subjects compared to healthy controls. Using a hand-held device (Micro-smokerlyzer, Bedfont, UK), exhaled CO was measured in mild CF subjects ($FEV_1 \geq 70\%$, n=7), severe CF subjects ($FEV_1 < 30\%$, n=6), and patients admitted with an infective exacerbation prior to administration of intravenous antibiotics (n=6). Compared to non-CF, non-smoking control subjects (n=8) with CO levels of 1.1 ± 0.4 ppm, levels were not significantly different in any CF group (1.5 ± 0.6, 1.2 ± 0.4, and 1.2 ± 0.4 ppm respectively). These values contrast with current smokers (n=5) who had CO levels of 24.5 ± 4.8 ppm. Thus, while measurement of BC NO_2^- is a potentially useful marker of lower airway inflammation in CF, additional measurements of NO_3^-, IL-8 or CO are unlikely to provide useful information.

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THE CHARACTERISATION OF *ACTIVE* MMP-2 AS A POTENTIAL TARGET FOR THERAPY IN CYSTIC FIBROSIS

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One of the major features of cystic fibrosis is the extensive damage to lung tissue by aberrant proteolysis. Whilst the majority of research to date has been concerned with the role of the granulocytic proteases, neutrophil elastase and cathepsin G, there have also been some reports which describe the presence of metalloproteases (MMPs) in the purulent sputum of CF patients. As MMPs are known to degrade elastin, collagen and other components of lung tissue, and can be activated in vivo by neutrophil and bacterial proteases, including those from *Pseudomonas spp.*, we wished to characterise those species which may be involved in the aetiology of CF. Unfortunately, reports describing the role of MMPs in CF have used traditional methods such as gelatin zymography or immunoassay to measure biological activity, neither of which is capable of truly discriminating between active and inactive forms of the enzymes. We have developed a novel affinity purification protocol using a potent, synthetic MMP inhibitor which *can only bind to the active forms of these enzymes.* This has enabled us, for the first time, to elucidate the role of *active* metalloproteolytic species in CF. As a result, we have shown that active gelatinase A (MMP-2) is present in high levels in purulent sputum of patients during active phases of the disease. Antiprotease therapy for CF, to date, has been entirely concerned with the development of synthetic or natural inhibitors of the serine protease, neutrophil elastase. Our findings, and the observation that synthetic inhibitors of MMPs are effective in the treatment of other severe inflammatory disorders, for example, rheumatoid arthritis and psoriasis, lead us to propose that such agents may also have considerable potential in preventing lung damage in CF. In addition, we propose that MMP-2 levels may prove to be a useful marker during aggressive episodes of the disease.

This work was supported by a BBSRC/DTI post-doctoral fellowship.

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THE USE OF FENTANYL AEROSOLS FOR THE RELIEF OF RESPIRATORY DISTRESS IN CYSTIC FIBROSIS

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Objective: To evaluate the effectiveness of nebulized fentanyl in cystic fibrosis (CF) patients with dyspnea from advanced lung disease.

Introduction: End of life issues are always difficult and emotionally charged for patients, their families and members of the health care team. Patients with CF are confronted with manifestations of pulmonary compromise with resultant respiratory failure. Health care professionals, in an effort to alleviate discomfort, prescribe symptomatic relief with systemic benzodiazepines and narcotics which may actually worsen respiratory function. Nebulized opioids have been used for several years in adult oncology patients as well as patients with non-malignant disease with the aim of decreasing the patient's perception of breathlessness. Morphine has historically been the narcotic of choice to provide both comfort and a moderate degree of pain control. Over the past four years in our institution, nebulized fentanyl has been used to treat the symptoms of dyspnea and anxiety associated with end stage cystic fibrosis.

Methods: Sixteen patients with advanced CF were treated with nebulized fentanyl during the time period from July 1995 through May 1999. Retrospective chart reviews, along with prospective patient interviews, were conducted to determine the effectiveness of delivering an opioid, namely fentanyl, via aerosolization. Objective data including PFTs, capillary blood gas monitoring and assessment of oxygen requirement were evaluated in certain patients. Subjective data, such as patient's perception of breathlessness and anxiety coupled with the observer's (physician, pulmonary nurse, clinical pharmacist or family member) perspective on effect were also considered.

Conclusions: Nebulized fentanyl was found to be a safe, effective and convenient pharmacologic intervention in the majority of the CF patients we treated. No patient reported discomfort directly related to the use of nebulized fentanyl. There was a reduction in the use of benzodiazepines as well as narcotics in the patients receiving nebulized fentanyl. Iatrogenic symptoms such as undue respiratory depression with a consequential rise in pCO2, CNS changes, sedation and constipation were prevented or at least minimized by the avoidance of systemic narcotic and/or benzodiazepine administration. Patients did not require intravenous access for nebulized fentanyl administration; therefore, potential cost reduction and use as outpatient therapy was feasible.

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EFFECT OF CHRONIC AZITHROMYCIN ON LUNG FUNCTION IN CYSTIC FIBROSIS

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Diffuse panbronchiolitis (DPB) and cystic fibrosis (CF) are both diseases characterized by chronic endobronchial infection with *Pseudomonas aeruginosa*, and intense airway inflammation. Chronic treatment with macrolide antibiotics has resulted in a dramatic improvement in survival in DPB by an anti-inflammatory mechanism. Macrolide antibiotics may be useful for chronic therapy in cystic fibrosis by slowing the progression of endobronchial destruction by anti-inflammatory and anti-bacterial mechanisms. We utilized chronic azithromycin therapy in 20 CF patients with very severe or rapidly progressive obstructive lung disease. Patients were treated for an average of 9.4 months (range = 2 - 18 months) with azithromycin (dose = 250mg every other day). Therapy was initiated at the end of a hospitalization for pulmonary exacerbation or in the outpatient clinic at a follow-up visit. All patients were infected with *Pseudomonas aeruginosa*. The mean FEV_1 at initiation of therapy was 0.94 ± 0.41L and at the end of therapy was 1.14 ± 0.51L, a 21% improvement in FEV_1 during therapy ($p = .0006$). Liver and renal functions were monitored closely during the study period. No patient suffered any significant side effects during the study period. Based on its theoretical efficacy and the potential role for chronic macrolide therapy in cystic fibrosis demonstrated by this data, we are conducting a randomized double blind, controlled trial to evaluate the effect of chronic azithromycin therapy on

lung function, inflammatory markers, and bacterial products in cystic fibrosis patients with mild to moderate obstructive lung disease. Supported by the American Lung Association.

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BRONCHOCONSTRICTION WITH NEBULISED COLISTIN IN CHILDREN WITH CYSTIC FIBROSIS

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Introduction It has previously been reported that nebulised therapies can have a bronchoconstrictive effect in adults. No reports to date however, have delineated the incidence and degree of possible bronchoconstriction in children with cystic fibrosis. **Methods** Children attending our tertiary cystic fibrosis centre were requested to participate in the study if they were currently taking colistin by nebuliser. Children were asked not to take regular bronchodilators for at least 6 hours prior to the test. Lung function tests were performed at baseline, and then at zero, 15 and 30 minutes post nebulisation of colistin; 1 megaunit, if ≥7 years, 0.5 megaunits if ≤6 years(total 4ml in 0.9% saline). Children demonstrating >10% fall in baseline FEV_1 were asked to return for a second study with a bronchodilator given before colistin. **Results** 24 children were studied (mean age 12.4 years, sd 3.2). Six children (25%) demonstrated a fall in FEV_1 >10% following colistin (5 maximal at 0 minutes, 1 maximal at 15 minutes post colistin). The mean change in FEV_1 for all patients was -4.2%, maximal fall 28.6%. All but one child had recovered to within 10% of baseline within 30 minutes. Six children, when asked, reported chest tightness; four of these had a fall in FEV_1 >10%. Two children to date have had a second study with bronchodilator, one continued to have a fall in FEV_1 >10%, but less marked than in the first study. **Conclusions** Bronchoconstriction occurs in a significant number of children following nebulised colistin, and symptoms alone are not adequate to identify them. Studies are continuing to identify how well bronchodilators can prevent constriction.

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THE USE OF DNASE IN DAILY CARE OF CYSTIC FIBROSIS: RESULTS OF A COHORT STUDY OF 199 PATIENTS IN 13 CENTRES

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Objective

Short-term clinical trials with DNase have shown minor to moderate benefits in cystic fibrosis patients. This study was performed to analyse the effectiveness of DNase in daily practice, and to obtain information on its effects in the long term and in different disease stages.

Methods

Patients that were being attended in 13 specialised units were included if they started DNase treatment before June 1996. Baseline data before DNase use and data during the DNase treatment period were recorded.

Results

199 patients were included in the study; 166 continued on DNase treatment when the data were collected. The mean age (95% CI) was 14,5 (13.7;15.2) years and 103 (51.8%) patients were female. The mean maximum improvement in FEV1 was observed during the first month of treatment [11.1%(6.1;16.1)]. By the end of the first and second year of treatment, mean changes in FEV1 were 3.3%(-1.1;7.6) and 5.1% (-0.7;10.9) respectively; at the end of the same periods, 34% of patients had improved their baseline FEV1 by 10% or more, but in around 50% of patients there was a decline below the baseline level. A large interindividual variability in pulmonary function changes after starting DNase treatment was documented. In addition, the medium-term response to treatment was correlated with early response during the first three months. Consistent changes were not found in exacerbation pattern during the first year of treatment.

Conclusion

The benefits of DNase use in daily practice are limited but apparently can be maintained in the medium-term. A large interindividual variability in response to DNase treatment has been documented and the benefits are doubtful in around 50% of patients. This observation points out the need for setting up a withdrawal trial in these patients using as an eligibility criterion the early response observed during the first three months of treatment.

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LONG-TERM STUDY OF RECOMBINANT HUMAN DNASE IN CYSTIC FIBROSIS PATIENTS: A FOUR YEAR FRENCH MULTICENTER STUDY

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Objectives: rhDNase, administered by aerosol inhalation, has been evaluated extensively for safety and efficacy in patients with CF, but little is known about its long-term effects. The objective of the present study is to describe retrospectively the long-term effect of nebulized rhDNase on pulmonary function and nutritional status.

Patients and methods: A total of 138 CF patients with mild to moderate lung disease (defined by a FVC ≥ 40 %) were recruited in March 1999 from 3 CF centers in Toulouse, Lille and Rennes (France). For each patient rhDNase (2.5 mg per dose) was administered once daily by a jet nebulizer (Hudson T-Up-draft II or Paris LC+) connected to an air compressor (Pulmo-Aide or Pariboy). The data retrospectively collected included patients demographics, FVC and FEV1, expressed as a percentage of the predicted value for height, age and gender, the body mass index (weight/height^2, BMI), expressed as a percentage of the 50th percentile for age and gender, and adverse effects. Data were collected one year before the onset of rhDNase, at the onset, and after 1, 2, 3 and 4 years of treatment. The mean duration of treatment was 40.5 months (range 12–54) and patients were reviewed every 3 months. Throughout the study, patients continued to receive standard care for CF. The statistical analysis was based on a Student t-test. Changes in pulmonary function tests were statistically significant when p value was lower than 0.05.

Results: 138 CF patients (74 males and 64 females), with an mean age of 13.2 years (range 7–25.5) and starting therapy at a median age of 8.9 years (range 5–20) were included. 123 achieved two years treatment, 89 three years and 75 four years. Two of the patients discontinued treatment because of hemoptysis, that resolved within 3 days. Treatment was well tolerated and adverse and transient events were limited to upper airway irritation in less than 5 % of the patients. Data are summarized as follows (see table):

The analysis of different sub-groups showed interesting results:

When the baseline FVC is ≤ 85% (47 patients, mean age at the onset of treatment 9.9 years), DNase prevents the pulmonary deterioration (initial FVC 73.9% and 76.3% after 4 years; initial FEV1 63.9% and 61.7% at end-point), and maintains nutritional status (initial BMI 89.6% and 91.6% after 4 years). When treatment is started at the age of 5 (early treatment), rhDNase prevents the decline of the pulmonary function (52 patients; mean age 5.3 years; initial FVC 99.7% and 96.1% after 4 years; initial FEV1 90.1% and 86.9% at end-point, p = 0.08). On the other hand, when it is started later (between the age of 6 and 10), when the pulmonary function starts to decline, the effect of the treatment is maintained over two years but diminishes after 3 and 4 years (56 patients; mean age 7.9 years at baseline; initial FVC 91.3% and 84.6% after 4 years; initial FEV1 84.2% and 76.5% at end-point, p = 0.05).

Conclusion: The present study confirmed rhDNase's long-term safety and efficacy in preventing the decline of lung function in CF. When it is started in children at the age of five, with normal pulmonary function tests (PFT), as it is done in our CF centers, the mean annual decline of FVC and FEV1 is moderate. In older children, with a baseline CVF ≤ 85 %, the PFTs and BMI also remain stable. Other studies are needed to determine on a larger scale if it is reasonable to start the treatment in any CF child at

the age of 5, even if the PFTs are still normal. Anyway it is clear that rhDNase must not be given routinely unless the response can be monitored objectively

	1 year before	Baseline	1 year	2 years	3 years	4 years
Mean BMI						
(%)	98.1	96.2	96.6	97	97.4*	97.9*
(SD)	*1.7*	*1.7*	*1.8*	*2.2*	*2.4*	*2.7*
(range)		*77–125*				
Mean FCV						
(%)	99.6	91.8	94.1	90.7	86.8**	86.3**
(SD)	*16.3*	*17.5*	*18.3*	*16.9*	*15.6*	*16.7*
(range)		*42–140*	*51–136*	*48–118*	*61–119*	*59–119*
Mean FEV1						
(%)	93.1	82.8	82.8	80.1	74.5**	75.1**
(SD)	*17.5*	*21.4*	*21.5*	*21.4*	*21.1*	*22.8*
(range)		*41–145*	*43–134*	*45–132*	*39–123*	*44–126*

*p=0.2; **p=0.01; ***p=0.05; ****p=0.08 (compared to baseline)

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EFFICACY OF DNASE IN INDIVIDUAL CHILDREN USING THE N-OF-1 STUDY DESIGN

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Large-scale, randomized, controlled clinical trials of DNase have not demonstrated consistent improvement in all patients studied. N-of-1 clinical trials may be useful in identifying patients who should receive DNase. We conducted randomized, double-masked, placebo-controlled, three period, multiple cross-over, 24-week, n-of-1 studies with DNase. Each of three consecutive, eight-week periods included four-week treatments with placebo and DNase administered in block random order. Children with CF 5 - 17 years old with an FEV_1 > 40% predicted and stable pulmonary status were eligible. Pulmonary function was evaluated at baseline and every four weeks. Change in percent predicted FEV_1 from baseline to the end of each four-week treatment was determined. The primary outcome measure was mean change in percent predicted FEV_1 while receiving DNase compared to baseline and placebo; a clinically significant change was set *a priori* at 7%. Analysis of FEV_1 results stratified children into four groups: a. "improved" (DNase values > 7% above baseline and placebo); b. "worse" (DNase values > 7% below baseline or placebo); c. "equivocal" (DNase values > 7% above baseline or placebo, but not both); and d. "no change" (< 7% change from baseline and placebo). Symptoms were assessed weekly using a visual analog scale and quality of life questionnaire. Physician confidence in study design and its clinical use was also examined. Of 20 children initially enrolled, 16 (mean age 10.2 years; range 5.8 - 16.8 years) completed the protocol (3 children had unstable pulmonary status at study initiation and were excluded; 1 child withdrew because of transportation problems). Four children "improved" (improvement above baseline 7 to 19%; improvement above placebo 9 to 13%). Four children were "worse" (decline below baseline -7 to -9%). Four children had "equivocal" results [three with improvement above baseline (7 to 14%), without improvement above placebo (0 to 5%); one without improvement above baseline (3%), with improvement above placebo (15%)]. In four children, there was "no change" (-2 to 4% from baseline; 0 to 5% from placebo). Data from overall well being and quality of life questionnaires were equivocal. All five participating physicians maintained a high level of confidence in study design and its clinical use. Based on these individual studies, 4/16 (25%) children should receive DNase. The n-of-1 study design is an effective decision making tool for assessing which children with CF benefit from DNase therapy.

Genentech supplied drug and placebo for this study.

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THE EFFECTS OF LOW FLOW OXYGEN AND BILEVEL VENTILATORY SUPPORT ON GAS EXCHANGE AND VENTILATION DURING SLEEP IN PATIENTS WITH CYSTIC FIBROSIS

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Introduction: We studied the effects of low flow oxygen (LFO_2) and bilevel ventilatory support (BVS), with or without additional oxygen, compared to breathing room air (RA) alone on ventilation, sleep architecture, oxyhemoglobin saturation (SaO_2), and transcutaneous carbon dioxide tension ($TcCO_2$) in patients with cystic fibrosis (CF) and severe lung disease. Methods: Six subjects, aged 27 ± 6.5 (mean ± SD), BMI 20±3kg/m^2, FEV_1 27±6 % predicted, FVC 45±9 % predicted, awake PaO_2≥ 67±8mmHg and $PaCO_2$ 47±6mmHg, underwent three sleep studies breathing, in random order, room air, LFO_2, and BVS±O_2 with continuous recording of SaO_2% and $TcCO_2$. On all three nights patients wore a nasal mask attached to a bias flow CPAP circuit. A baseline pressure of CPAP of 4–5cmH_2O was used each night. Minute ventilation (V_I) was measured via a pneumotachograph in the circuit. Sleep arousal and respiratory disturbance indices (RDI) were calculated. ANOVA with repeated measures was used to analyse the ventilation data, and Friedmans 2 way ANOVA was used with the $TcCO_2$, SaO_2, and RDI data. Results: V_I (litres/min)was reduced on the RA night from awake (9.9±2) to REM (7.2±2)($p<0.05$) and from NREM(9.3±1) to REM ($p<0.05$). On the LFO_2 night 1.4±0.7LO_2/min was required to maintain SaO_2 ≥90% and V_I was reduced from awake (9.7±3) to REM (7.5±3)($p<0.05$) and from NREM (9.7±3) to REM ($p<0.05$). This reduction in V_I from NREM to REM was mainly due to a decrease in tidal volume. On the BVS night pressures were IPAP 12.2±1, EPAP 4.5±0.8 and four of the six patients required additional O_2 with a mean requirement of 1.1±0.8L/min to maintain SaO_2 ≥90%. There was no significant difference in V_I between NREM (9.6±2) and REM (8.8±1) sleep when using BVS, although there was still a reduction in V_I from awake (10.6±1) to REM sleep ($p<0.05$). On the RA and LFO_2 study nights, RDI was highest during REM sleep and was associated with hypopneas. With BVS±O_2 there was a reduction in overall RDI and in REM RDI ($p<0.05$), which was not seen when on oxygen therapy alone. Both BVS and LFO_2 improved nocturnal SaO_2, especially during REM sleep ($p<0.05$). There was a trend toward attenuation of the rise of $TcCO_2$ seen in REM with BVS ($p<0.1$). Discussion: The most marked respiratory disturbance was seen in REM sleep with hypopneas and a reduction in V_I. BVS±O_2 was the only intervention which reduced the overall RDI and maintained V_I from NREM to REM.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS) IN CHILDREN WITH CYSTIC FIBROSIS (CF): IMPACT ON LUNG DISEASE

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PURPOSE: To describe the impact of FESS on pulmonary disease in children with CF and chronic sinusitis.

METHODS: Records of patients that underwent sinus surgery at St. Louis Children's Hospital were reviewed. Lung transplant patients were excluded.

RESULTS: 23 patients underwent sinus surgery: 5 were excluded for prior FESS elsewhere (3), not FESS (1), no pulmonary function (PFT) data (1). Mean age 7.3 yrs. (range 3 to 17 yrs.). All patients failed medical therapy consisting of antibiotics, intranasal steroids, nasal irrigation and usual CF care. Pansinus opacification was documented by computerized tomography in all, 2 with bulging of lateral nasal wall. Signs and symptoms of nasal obstruction predicted all cases with polyps (7/7). Other symptoms in-

cluded: purulent drainage (14, 3 with polyps), headache (3), cough (3), halitosis (1), poor appetite (1).

Microbiology analysis revealed that intraoperative cultures were not obtained in 3, coagulative negative staphylococcus was present in 8, nontypable hemophilus influenzae in 1, and no patients harbored anerobic organisms or fungal elements. 4/15 had methacillin-sensitive staphylococcus aureus, but only one had this organism preoperatively. 12 patients had Pseudomonas Aeruginosa (PsA) preoperatively: intraoperative cultures revealed 6 without PsA, and 6 with PsA that was either more sensitive or had an equivalent antibiogram.

There were 0.7 courses one year before and 1.2 courses one year after FESS of intravenous antibiotics per patient for pulmonary exacerbations. PFT obtained 1 month preoperatively were compared to those one year postoperatively. Forced vital capacity dropped from a mean of 113% predicted to 103, forced expiratory volume in one second (FEV1) from a mean of 122% predicted (range 56–312) to 100 (range 53–158). 6/18 had no significant worsening at one year (mean improvement 0.7% predicted, range 8 to -2).

4 patients required revision FESS for recurrent sinus symptoms 3.2 years later (range 1.4 to 5.2 years). All patients operated on prior to 1996 have received FESS revisions.

CONCLUSION: FESS doesn't significantly improve FEV1 or decrease the need of intravenous antibiotics for pulmonary exacerbations. Consideration of tailoring antibiotic therapy to provide better coagulative negative staphylococcus coverage may help improve symptoms and delay the need for FESS.

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A PILOT STUDY TO EXAMINE THE EFFECT OF NEBULISED HYPERTONIC SALINE IN INFANTS WITH CYSTIC FIBROSIS

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Lung disease in CF is characterised by obstructive airways disease with viscid mucus, reduced mucociliary clearance and a cycle of pulmonary infection and inflammation that leads to progressive lung damage. Hypertonic saline (HS) has been shown to enhance mucociliary clearance in adults and young people with CF. Analysis of our longitudinal study of lung function in CF infants demonstrated reduced specific respiratory system conductance (sGrs) and increased respiratory system resistance (Rrs) compared with healthy controls from 3 months of age. We postulated that the use of hypertonic saline in infants might improve mucociliary clearance and lead to improvement in airways obstruction as measured by Rrs and sGrs in infants with CF. **Aims:** To determine whether nebulised HS was tolerated and assess a potential effect on lung function in infants with CF. **Methods:** Five infants consecutively diagnosed through the neonatal screening program in Queensland, who were homozygous for the ΔF508 mutation, were enrolled. Infant pulmonary function was measured using the SensorMedics 2600 Pulmonary Function Cart. Three baseline lung function measurements were taken at two-week intervals. At the third baseline visit nebulised salbutamol and sodium cromoglycate twice daily prior to chest physiotherapy were introduced. Two weeks later, lung function was measured and hypertonic saline 6% (HS) was started. HS was administered as 8ml nebulised twice daily via a Microneb ultrasonic nebuliser after nebulised salbutamol and sodium cromoglycate around 30 minutes prior to chest physiotherapy. This regime was continued for 3 weeks and lung function was again measured. HS was then ceased and lung function measured again 2 weeks later. Parents were asked to keep a symptom and drug diary and medication bottles were returned at each time point for assessment of compliance. **Results:** All parents noticed increased cough with chest physiotherapy after HS but not after salbutamol and sodium cromoglycate. No infant stopped HS during the study and it was well tolerated. There was no demonstrable change from baseline in sGrs or Rrs throughout the study. **Conclusions:** Nebulised HS was tolerated and increased cough during chest physiotherapy. There was no change in lung function in the infants studied.

Supported by Cystic Fibrosis Research Inc. Queensland.

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THE ROYAL BROMPTON HOSPITAL CF DATABASE. COLONIZATION WITH *Ps aeruginosa* AND THE EFFECT OF AEROSOLIZED ANTIBIOTICS ON THE RATE OF LUNG FUNCTION DECLINE IN ADULT PATIENTS WITH CYSTIC FIBROSIS

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The main cause of morbidity and mortality in CF patients is as a result of severe chronic lung infection caused by *Ps aeruginosa*. Regular treatment with aerosolized antipseudomonal antibiotics now represents a cornerstone of respiratory therapy. 1036 patients with cystic fibrosis were seen at The Royal Brompton Hospital between 1965 and 1997. The results of the patient annual review, which describes changes in symptomatology, physical examination, social circumstance, drug therapy, lung physiology, respiratory microbiology, biochemical and hematological parameters, are transferred to an electronic database (Microsoft SQL Server 7.0®) to be made available for subsequent analysis using a statistical package, Data Desk®. A study was undertaken in order to describe the mean age of colonization by *Ps aeruginosa*, the proportion of colonized patients (currently attending the clinic) receiving aerosolized antibiotics and the effect of aerosolized antibiotic therapy on the rate of decline of lung function. All patients colonized with *Ps aeruginosa* and receiving aerosolized antipseudomonal antibiotics were included in this analysis. Data from patients who have undergone transplantation were included only up until the time of the transplantation procedure. 938 (90.5%) of the 1036 studied were colonized with *Ps aeruginosa*. The mean age at which colonization with *Ps aeruginosa* occurred was 16.55 years. Of 508 colonized patients currently attending the clinic, 392 are currently receiving aerosolized antipseudomonal antibiotic therapy. A linear regression found that of this contemporary population, FEV_1 percent predicted decreased at a rate of 0.99% per year, which is better than would be expected for this patient population. While no formal comparison is possible at this stage, this observation supports the further study of long-term use of aerosolized antipseudomonal antibiotic therapy in adult CF patients colonized with *Ps aeruginosa*.

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COMPARISON OF AIRWAY PRESSURE AND OSCILLATION FREQUENCY OF FOUR AIRWAY CLEARANCE DEVICES

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BACKGROUND: Factors that improve mucus clearance rate are important for patients with cystic fibrosis. Studies have shown that high frequency oscillation enhances tracheal mucus clearance. Comparison of airway pressure waveforms and oscillation frequency for four airway clearance devices was recorded to compare the operational characteristics of intrapulmonary percussion effects.

METHODS: Each device was connected to a pressure transducer on the mouthpiece and pressure waveforms were recorded using a computer sampling at 300 Hz. Devices were operated by a trained respiratory care practitioner and pressure waveforms were recorded.

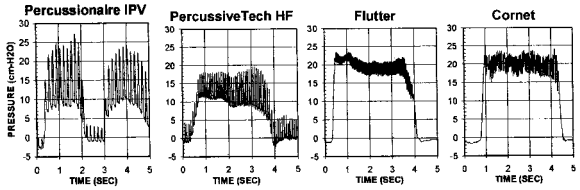
RESULTS: The results of this evaluation are summarized below with pressure waveforms (see Table).

DISCUSSION: The results indicated that peak pressure for all devices ranged from 15–26 cm-H_2O depending on the devices, setting and patient exhalation effort. However, the pressure amplitude varied greatly for devices using external gas source (8–17 cm-H_2O) vs. patient's own effort (2–7 cm-H_2O). The oscillation frequencies also vary greatly with these two classes of devices.

CONCLUSIONS: These results suggest that patient's own effort can generate high frequency airway oscillation, but very little pressure amplitude is generated. Devices with external gas source can generate significant pressure amplitude, which may be beneficial along with the high frequency airway oscillation.

Supported by VORTRAN Medical Technology 1, Inc.

Device	Peak Pressure (cm-H_2O)	Amplitude (cm-H_2O)	Frequency (cycle per minute)
Percussionair® IPv®	17–26	10–17	360–540
PercussiveTech HF™	15–19	8–11	720–840
Flutter®	20–24	2–5	1200–1800
Cornet™	15–23	3–7	1080–1700



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VALIDATION OF AN INSTRUMENT MEASURING PATIENT SATISFACTION WITH CHEST PHYSIOTHERAPY (CPT) TECHNIQUES IN CYSTIC FIBROSIS (CF)

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CPT has been an integral part of CF care for over 40 years. Recently, alternative techniques were introduced that may differ from standard CPT with respect to patient satisfaction, perceived costs, and benefits. Patient satisfaction and perceived efficacy are thought to be related to compliance with prescribed therapies. No tested instrument has been reported to measure patient satisfaction with various CPT techniques. We developed a CPT satisfaction questionnaire that was first piloted with 24 patients in a clinical trial comparing three CPT techniques. To more fully evaluate performance of this measure, we conducted a larger cross-sectional study. Psychometric analyses included itemetric performance, confirmatory factor analysis based on a priori groupings, test-retest reliability, and comparison by disease severity and compliance. The CPT satisfaction survey consists of 17 items with 4 dimensions: efficacy, convenience, comfort, and overall. If more than one CPT technique was used, patients were asked to complete a survey for each. Items were summed and averaged for a total score. A second form asked about perceived disease severity, importance of chronic therapies, and current home use patterns. Satisfaction and attitude items were rated on a five-point Likert-type scale. Questionnaires were mailed to 349 CF patients/primary caregivers in one CF Center. There were 17 returned as undeliverable and 129 (39%) completed and returned. The survey was sent to 20 subjects for test-retest reliability. Responding subjects included 66 males vs. 63 females and ranged in age from 2 months to 47 years. Distribution of disease severity (self-rated) was 60 mild, 47 moderate, 14 severe. Available FEV_1 data (n=82) showed a range of 21–155% of predicted (mean 76%). 79 subjects used PDPV, 21 Flutter, and 14 HFCWO. Five used more than one technique. Internal consistency analysis found an overall coefficient alpha of .87 (range .74-.89 for 4 domains). As anticipated, factor analysis demonstrated domains for efficacy, convenience, comfort and general satisfaction. Mean total satisfaction scores were significantly different among therapies (R^2=.118; F(3,120) = 5.33; p=.0018): PDPV =3.75, Flutter = 4.30, HFCWO = 4.12. Significant differences were also observed for convenience and overall sub-scores, but not efficacy and comfort. Linear correlations between perceived disease severity and the importance of CPT and breathing treatments were identified. The importance of enzymes, vitamins, Pulozyme, and inhaled antibiotics did not differ linearly by disease severity. Disease severity was positively correlated with CPT compliance. These results suggest that the CPT satisfaction questionnaire has good reliability and content validity. Significant differences in patient satisfaction exist for therapies. This measure will be a useful adjunct outcome measure in clinical trials evaluating current or new CPT techniques.

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MECHANICAL VENTILATION (MV) DUE TO ACUTE RESPIRATORY FAILURE (ARF) IN CYSTIC FIBROSIS (CF): OUTCOME ANALYSIS AND CASE-CONTROL STUDY

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Historically, the outcome for CF patients requiring mechanical ventilation due to acute respiratory failure has been quite poor and most management efforts have been palliative. Advances in ventilator management and critical care medicine have improved MV outcomes for patients with other chronic and acute respiratory diseases. Assisted ventilation for ARF in CF patients has not been reviewed in 20 years and it is unknown whether these advances have impacted on mortality of CF patients requiring MV. We evaluated our experience over a 10-year period and attempted to identify factors associated with a poor outcome and those leading to ARF requiring MV. Charts for all CF patients requiring MV for ARF between 1988 and 1998 were reviewed and pertinent data extracted. Cases were then matched with controls for gender and age. Data regarding steroid use, FVC, FEV_1, microbiology, nutritional status, CF related diabetes (CFRD), liver dysfunction, and a history of massive hemoptysis (HEM) or pneumothorax (PTX) were analyzed. 38 episodes of MV were identified in 33 subjects. Only the first episode was included in analysis. Nine subjects were <5 years of age (mortality = 22%), nine were 5 to 15 years (mortality = 67%), and fifteen were >15 years (mortality = 80%). Demographic data are summarized below. Steroid use (odds ratio [OR] = 5.5), CFRD (OR = 4.4), and history of HEM (OR = 3.4) or PTX (OR = 3.1) suggested an increased risk of mortality once MV was instituted. The case-control analysis indicated a markedly increased risk of developing ARF requiring MV for individuals with a history of HEM (OR = 6.3) and % ideal body weight <80% (OR = 4.2). Individuals using steroids and those with CFRD may have a slightly increased risk of requiring MV (OR = 1.4 and 1.8, respectively). Advances in MV and critical care medicine have not significantly affected the mortality of CF patients requiring MV due to ARF. Infants and young children have a favorable prognosis whereas those ≥ 5 years of age have significantly higher mortality. Steroid use, CFRD, and a history of HEM or PTX suggested an increased risk of mortality. Malnourishment and history of HEM are important risk factors for having an episode of ARF leading to MV.

	Survivors	Non-Survivors	P value
Gender (male/female)	8/5	11/9	0.9
Steroids	1/13 (8%)	7/20 (35%)	0.1
FEV_1 (percent predicted)	35±23	34±16	0.9
CFRD	1/13 (8%)	6/20 (30%)	0.2
History of HEM	3/13 (23%)	7/20 (35%)	0.7
History of PTX	1/13 (8%)	5/20 (25%)	0.4
Ideal Body Weight < 80%	9/13 (69%)	14/20 (70%)	0.7

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A RANDOMISED CONTROLLED STUDY OF IN-HOSPITAL EXERCISE TRAINING PROGRAMS IN CHILDREN WITH CYSTIC FIBROSIS(CF)

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Objective: To compare in hospital exercise training programs in terms of their effect on spirometry, aerobic capacity, weight gain, lower limb strength and quality of life.

Rationale: Fitness, as measured by maximal aerobic capacity, is an independent predictor of survival. Although previous studies have demonstrated that exercise training programs benefit patients with CF, there are no studies comparing aerobic training with resistance training in children with CF. The program undertaken by patients is often based on the personal preference of the clinician, physiotherapist or child. This study compares aerobic training (AT), resistance training (RT) and no specific training programs in children with CF.

Method: 66 children aged 8 to 16 years, with a wide range of disease severity, were randomised into AT, RT or no specific training (control) programs when admitted to hospital with intercurrent chest infections. While

in hospital, the children received standard chest physiotherapy and appropriate intravenous antibiotics. Each child received a minimum of 30 minutes of supervised training, 5 days a week. A treadmill exercise test, spirometry and lower limb strength assessment (using the Cybex dynamometer) were performed on admission, discharge and 1 month post discharge from hospital. A validated Quality of Well Being Scale was completed on admission and 1 month post discharge from hospital.

Results: The mean duration of admission was 18.7 days (range14–36 days). Student's T test and ANOVA (Duncan's Post Hoc test) were used to analyse the results. Improvement in QoL and VO2 was greatest with AT (p0.01). The mean (+/- 1 SD) percent change in QoL was +14.28, +2.54, -0.38 (+/-2.9) for AT, RT and control groups, respectively, and for VO2, +21.64,+2.14,-3.58 (+/-6.46) for AT, RT, and control groups. Improvement in FEV1, weight gain and strength was greatest with RT (p0.01). The mean percent change in FEV1 for AT, RT and control was +6.54,+10.09,+2.51 (+/-7.76) respectively and +2.09,+7.34,+2.81 (+/-2.34) mean percent change in FEV1 for AT, RT and control was +6.54,+10.09,+2.51 (7.76), respectively, and +2.09,+7.34,+2.81 (2.34) mean percent change in weight in the same groups. Aerobic capacity correlated more strongly than FEV1 with QoL Pearson's r 0.57 vs 0.32. p0.01).

Conclusions: The choice of training program would depend on the individual goals of the patient and clinician. If a better quality of life or aerobic capacity is sought, aerobic training should be undertaken. If weight gain or better FEV1 is sought, resistance training should be undertaken. Further studies on the benefit of combining the two programs are needed.

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EXERCISING DESPITE A LOW FEV1; ADAPTATIONS DURING EXERCISE IN CYSTIC FIBROSIS

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Patients with advanced CF lung disease and low FEV1 sometimes enjoy surprisingly active lifestyles, including full-time employment and vigorous recreational exercise. To investigate exercise adaptations in CF we performed progressive cardiopulmonary cycle exercise tests measuring oxygen consumption (VO2), ventilation, oxygen saturation and end-tidal CO2 (PetCO2) in 46 adult CF patients (mean age 28.4 years, range 15–51). Maximum VO2 during exercise was impaired (average 77 ± 19(sd) % predicted) but was less abnormal than FEV1 (mean 55 ± 27(sd)% predicted), with considerable discordance between these parameters (R=0.46). Desaturation of 3% or more at peak exercise occurred in 17 of 46 tests, and appeared linked to the degree of obstruction; peak exercise saturation below 90% was only seen when FEV1 was below 40% predicted. CO2 retention on exercise (measured indirectly as PetCO2 >= 45mmHg) occurred in 12 patients. Without arterial sampling we cannot to say how many additional patients had arterial hypercapnia which was not (because of parallel dead space) reflected in high PetCO2. During submaximal work (40% predicted VO2max), measured ventilation exceeded predicted ventilation in 38 of the 44 patients who achieved this workload (mean 123 ± 22(sd)%), even in those with severe airflow obstruction. This relatively increased ventilation during submaximal exercise is likely to represent dead space ventilation (high V/Q lung units) while the desaturation results from low V/Q units. The ventilatory response at maximal exercise was examined by dividing the increase in ventilation from rest to peak exercise by the corresponding increase in VO2 (dVe/dVO2). High PetCO2 was only seen when the increase in ventilation was less than 33 l/min per l/min VO2. This relative underventilation at peak exercise was not simply due to patients reaching their predicted maximum ventilation. Underventilating and allowing pCO2 to rise during exercise may be one adaptive mechanism used by patients to minimise respiratory work in the face of airflow obstruction. There was a weak but significant positive correlation between nutritional state (body mass index) and VO2max (R=0.38). These results illustrate the poor correlation between exercise capacity and spirometry. Many patients achieve more exercise than expected by tolerating levels of desaturation and CO2 retention which would cause significant discomfort in normal subjects. We conclude that a history of continued physical activity may mask important physiological derangements revealed only by exercise testing. Formal exercise testing is useful in identifying these problems and may assist in deciding when patients should be referred for transplantation.

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GASTROESOPHAGEAL REFLUX DURING CHEST PHYSIOTHERAPY: A COMPARISON OF POSITIVE EXPIRATORY PRESSURE AND POSTURAL DRAINAGE WITH PERCUSSION

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A high incidence of gastroesophageal reflux (GER) is known to occur in patients with cystic fibrosis and has been reported to be exacerbated by chest physiotherapy consisting of head down postural drainage positions combined with percussion. The purpose of this study was to evaluate the effects on GER of chest physiotherapy performed using the Positive Expiratory Pressure Technique (PEP) in an upright position compared to standard Postural Drainage and Percussion (PD&P). 10 patients (mean age 13.2 years) with cystic fibrosis and suspected GER underwent oesophageal pH monitoring for a period of 48 hours. During this period patients received four sessions of chest physiotherapy consisting of two sessions of PD&P performed in gravity assisted positions and two sessions of PEP performed in an upright position. Patients were randomized as to which order treatments were performed. During the background period, the number of reflux episodes per hour was significantly greater during the day in the upright position (mean 14.0±8.7) compared to sleep in the horizontal position (mean 4.0±2.2) in 8/10 patients (p less than 0.01). During both PD&P and PEP the number of reflux episodes and Fractional Reflux Time were both significantly increased, but there was no signifcant difference between either the PD&P and PEP sessions. On further examination of the data, the reflux episodes in both groups appeared to be associated with cough. The physiotherapy was performed according to standardized procedures for each method. As part of each physiotherapy session, patients were instructed to huff and cough during each postural drainage position and with each PEP cycle. Previous studies have not reported this association. The effects of cough on GER needs to be further evaluated.

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DETERMINANTS OF INTRAVENOUS (IV) ANTIBIOTIC TREATMENT INDUCED CHANGES IN DISABILITY IN ADULT CF

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We have previously shown that treatment induced changes in disability as measured by the modified shuttle test (MST), are poorly related to spirometric measures of lung function. The aim of this study was to investigate the extent to which treatment induced changes in exercise capacity are influenced by other measures of disease impairment and by quality of life (QoL). Eighteen patients with mild to moderate CF disease (FEV_1 % predicted >25%), mean (SD) age 29 (4) years, each undergoing intravenous (IV) antibiotic treatment for an acute exacerbation of respiratory disease. The data collected at the beginning and at the end of IV antibiotic treatment included, 24 hour sputum volumes, mean overnight heart rate, CRP level, resting SaO_2, body weight, exercise capacity (MST distance), QoL (chronic respiratory disease questionnaire, CRDQ) and FEV_1 % predicted. There was a significant improvement in all measurements ($p<0.05$) following IV antibiotic therapy. Standardised response means showed that all measurements (FEV_1 % predicted=1.03; MST distance=1.12; 24 hour sputum volume=1.22; body weight =0.70; mean overnight heart rate=0.67; CRP=0.78; QoL=1.28) were sensitive to IV antibiotic treatment. A reweighted squares stepwise regression model was used to retrospectively evaluate the % of variance in treatment induced change in MST distance (dependent variable) that could be explained by change in other measures (predictor variables). Five predictors explained 87.5% of the variance in change in MST distance. Change in QoL, mean overnight heart rate and CRP contributed to the vast majority of the explained variance, with change in body weight and SaO2 adding an additional 17%. If FEV_1 had been forced into the regression model its standardised coefficient would have been -0.137 with a partial correlation of 0.37, which was much lower than those variables included in the model. These findings are significant because they indicate that spirometry contributes little to the % of explained variance in change in exercise capacity and therefore exercise capacity must be measured directly in order to evaluate comprehensively the outcome of treatment on disability in CF.

The results also indicate that IV antibiotic treatment induced changes in exercise capacity are influenced by a range of factors including sputum production, systemic inflammation, nutritional status and QoL.

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AIRWAY CLEARANCE TECHNIQUES (ACTS) AND EXERCISE IN ADULT CYSTIC FIBROSIS- A SURVEY OF PATIENT BELIEFS, KNOWLEDGE AND ADHERENCE

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It has been proposed that patient beliefs and knowledge of the effectiveness of treatment are important determinants of overall adherence to airway clearance and exercise regimes. We carried out a postal survey using the questionnaire developed by Carr et al., (1996) to investigate: 1-what physiotherapy techniques are used by adult patients; 2-patient beliefs about the efficacy of ACT and exercise; 3-if there was an association between individual beliefs and adherence. Questionnaires were sent out to all patients attending the adult CF centre (n=78) and were returned by 62 (80%) of patients. Patients used a diversity of ACTs (active cycle of breathing technique, 33/62 (53%), PEP mask, 17/62 (27%), clapping, 14/62 (21%), flutter 2/62 (3%), and autogenic drainage 1/62 (2%)). Forty-three patients stated that ACTs were important to their sense of well-being and 39/62 (62%) of patients agreed that ACTs prevented their chest deteriorating. More patients found physiotherapy helpful when they were unwell (59/62, 93%) than when they were well (47/62, 75%) and consequently a number of patients 18/62 (25%) did not adhere to a daily airway clearance regime. The main reasons reported for non-adherence to ACT included "not enough time" and "not necessary if you do regular exercise." In fact 15/62 (23%) felt that airway clearance could be substituted by exercise all the time, 30/62 (46%) some of the time, and only 13 (21%) of patients felt that regular physiotherapy was important and should never be substituted by exercise. 22/31 patients with moderate to severe disease (FEV_1% predicted <70%) felt that ACT could be substituted with exercise when well or even all the time. Of the 44/62 (71%) of patients who do daily airway clearance 25/62 (39%) do ACT once a day, 13/62 (30%) do ACT twice a day and 6 (9%) do three treatments per day. The most common reason for performing ACTs regularly was that it " kept the chest clearer and healthier." There was a moderate relationship between how important physiotherapy was thought to be and how often physiotherapy was performed every day (r=0.40, p=0.02). Patients' beliefs on the benefits of ACT were generally positive. In spite of the attempts made to tailor the prescribed ACT to the individual needs of the patients, some patients still find ACT very time consuming and many patients are substituting regular physiotherapy with exercise. These findings have important implications for clinical practice. (Carr et al., Physiotherapy, 1996: 82; 621–7)

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THE EFFECTS OF STANDARD AND MODIFIED PHYSIOTHERAPY POSITIONS AND STATES OF AROUSAL INCLUDING NON-NUTRITIVE SUCKING, CRYING AND SLEEP ON GASTROESOPHAGEAL REFLUX IN YOUNG INFANTS WITH CF

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Infantile reflux is common in early life, resolving in most normal infants by 12–24 months. Numerous researchers have found gastroesophageal reflux (GER) is more common in CF. Non-nutritive sucking (NNS), crying (C) and falling asleep (FA) are common during chest physiotherapy (CPT). Aims: to determine the incidence of GER in specific widely used CPT positions; to establish whether different states of arousal (SOA) are associated with increased GER during CPT. Methods: Twenty infants with CF, mean age of 2.1 months, were studied during 2 sessions of SPT and 2 sessions of MPT on two consecutive days during 30 hour esophageal pH monitoring. SPT consisted of supine horizontal [S-], prone [P-30°], left [LSL-30∞] and right side lying [RSL-30∞] each with 30° head down tilt. MPT consisted of supine 30∞ head up tilt [S+ 30°], prone [P-], left [LSL-] and right side lying [RSL-] all horizontal. First, the number of reflux episodes (NRE) were calculated in each position during 8 minutes of percussion and vibrations on two separate occasions on consecutive days. Second, the SOA was recorded during each CPT position. The SOA were 1-asleep; 2-asleep with NNS; 3-awake; 4-awake with NNS; 5-crying. The reflux ratio (RR) which was the NRE proportional to the period of time in that SOA was calculated for each SOA. The higher the RR the greater the proportional amount of reflux recorded in that SOA. Results: The total NRE for all 20 infants recorded during MPT was 47 episodes versus 69 during SPT, p=0.029*. The NRE in each position during MPT vs SPT were: [S+ 30°]=16 vs [S-]=27 episodes, p=0.067; [P-]= 9 vs [P-30°]=20, p=0.03*; [RSL-]=9 vs [RSL-30°]=14, p=0.45; [LSL-]=13 vs (LSL-30°)=8, p=0.59. The total percent time (MPT and SPT) the 20 infants spent in each arousal state was: 1-asleep=14%; 2-asleep with NNS=24%; 3-awake=23%; 4-awake with NNS=21%; 5-crying=18%. The reflux ratio (RR) calculated during each state of arousal during MPT vs SPT, respectively, were: 1-asleep=1.00 vs 1.20; 2-asleep with NNS=0.60 vs 0.41; 3-awake=1.31 vs 1.59; 4-awake with NNS=1.28 vs 0.88; 5-crying=0.64 vs 1.15. Conclusions: There were significantly more reflux episodes recorded during total SPT vs MPT. Furthermore, [P-30°] had significantly greater NRE than [P-]; there was a higher NRE during [S-] versus [S+30°]and [RSL-30°] versus [RSL-]. The lowest RR was recorded during sleep with NNS. The RR during crying during SPT was high compared to MPT. Sleep and NNS were not found to increase GER during CPT.

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REPEATED INSPIRATORY MANOEUVRES AGAINST A FIXED RESISTANCE WITH BIOFEEDBACK IS MORE EFFECTIVE THAN STANDARD CHEST PHYSIOTHERAPY IN AIDING SPUTUM EXPECTORATION IN CYSTIC FIBROSIS

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The purpose of this study was to compare the effect upon sputum clearance of the Test of Incremental Respiratory Endurance (T) (Ionescu et al Am J Respir Crit Care Med 1998;158:1271–1276 [1]) with supervised chest physiotherapy (P) in a group of twenty adult cystic fibrosis patients (10 females Mean FEV1 55% predicted, SD 24). Patients were randomly allocated to T or P on four alternate days at the commencement of treatment for an exacerbation of respiratory systems. T was performed at 80% of sustained maximal inspiratory pressure until failure and sputum was collected during the session and for a further 30 minutes. P comprised a supervised 30 minute treatment session including postural drainage, percussion and the forced expectoration technique. This was followed by 30 minutes post-treatment expectoration. Data were log transformed for statistical analysis. Sputum clearance was increased after T compared with P. (Table). The patients included eleven with low lean body mass (LBM). There was a positive correlation between LBM, FEV1 and inspiratory muscle function p<0.001[1]. In those subjects with low LBM there was an inverse correlation between FEV1 and the total protein and elastase expectorated during T and P, (p<0.01 and p<0.05, respectively, for both). Hence T and P were not limited by disease severity as indicated by FEV1 and low LBM. Repeated inspiratory manoeuvres can therefore be used in patients with CF because the level of effort is set to the individual's capacity and maintained using biofeedback. We conclude that T is more effective than standard P in mobilising sputum for expectoration during single treatment sessions.

LSN and AAI - supported by CF Trust UK.

	TIRE	TIRE	PHYSIO-THERAPY	PHYSIO-THERAPY
Weight g	7.6**	5.0, 11.5	4.8	2.1,11
Protein mg	97.7*	63.1, 155	50.1	25.7, 100
IL-8 ng	2.75*	1.48, 5.13	0.98	0.42, 2.29
Elastase µg	339	200, 617	178	79, 389

*Geometric mean and 95% confidence intervals. * p<0.05 **p<0.001*