**THE NEW MILLENNIUM CLINICAL 2008**


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This is the most recent installment of an extended open study of oral prophylactic treatment with egg yolk antibodies against *Pseudomonas aeruginosa* (anti-*Pseudomonas IgY*) of 17 Swedish patients with CF. They have been on prophylactic IgY treatment for up to 12 years and altogether for the equivalent of 114 patient years. A group of 23 Danish CF patients served as controls. There has been a total absence of adverse events. Only 29 cultures have been positive for *P. aeruginosa* (cultures after chronic colonization not included), that is, 2.3/100 treatment months compared to 7.0/100 months in the control group (P = 0.028). In the IgY treated group only one pair of siblings (2/17) has been chronically colonized with *P. aeruginosa* compared to seven patients (7/23) in the control group. Atypical mycobacteria, *S. maltophilia*, *A. xylosoxidans*, and *A. fumigatus* have appeared only sporadically. There have been no cultures positive for *B. cepacia*. There was no decrease in pulmonary functions within the IgY group. Body mass index values were normal or close to normal for all IgY treated patients. In conclusion, Anti-*Pseudomonas IgY* has great potential to prevent *P. aeruginosa* infections.

Hans Kollberg has relentlessly pursued the value of gargling with Anti-*Pseudomonas IgY* as a preventive treatment against *Pseudomonas* and the progress is recorded in a number of publications (Carlander D et al. Immunol Res 2000; 21:1-6. [PubMed] Carlander D et al, Biodrugs 2002; 16:433-437 [PubMed];Kollberg H et al, 2003 above; Nilsson et al, 2007 above). However, it must be observed that the numbers are small and the cruel lesson of the anti-*Pseudomonas Aerugen* vaccine trial comes to mind where an initial small study showed definite benefit but a large multicentre trial was quite negative.


Liver disease is an important cause of death in adults with cystic fibrosis. Ursodeoxycholic acid (UDCA) may slow progression. Managing varices and timely evaluation for liver transplantation are important. 154 patients attending the CF Centre at Papworth, Cambridge in the UK were followed for a median 5 years. 43 had significant liver disease. Only one patient developed chronic liver failure and none required liver transplantation. 27 underwent endoscopy; 1 required variceal banding, the others had insignificant varices. Ultrasound was normal in 97 patients while five had steatosis; nine further patients had splenomegaly but no other evidence of portal hypertension. Neither spleen size nor platelet count correlated with portal hypertension. So liver disease was common in adults with CF but disease progression was rare.

Thus liver disease detected and closely monitored in adults appeared to have a milder course than in childhood CF. Splenomegaly, unrelated to portal hypertension may be a consequence of the cystic fibrosis.
Dr Di Bilton was previously centre director of this adult CF centre at Papworth, Cambridge and in 2008 she moved to Royal Brompton Hospital London. She is a leading figure in UK CF care and research.

Most parents displayed erroneous beliefs regarding P. aeruginosa (PA) infection. Families performed a mean of 11 different hygienic measures, e.g. they prevented their child from being the first person to use the bathroom in the morning (72%) or from bathing in gravel pits and standing water (52%). The majority of parents felt markedly (44%) or somewhat (44%) stressed that their child might acquire PA, and many parents felt markedly (16%) or somewhat (43%) restricted and stressed by the hygienic measures. Less stressed parents tended to have more knowledge and undertook fewer measures.

The authors suggest that when informing and teaching parents on the nature of PA infection, caregivers should provide clear recommendations on reasonable actions to be taken. Also, physicians should anticipate and adequately respond to parental fears and misconceptions.

Genotypic identification and pathogenicity characterization were performed on B. cepacia complex isolates from the rhizosphere of onion and organic soils in Michigan. A total of 1,290 isolates, 980 rhizosphere and 310 soil isolates, were assigned to the species B. cepacia (160), B. cenocepacia (480), B. ambifaria (623), and B. pyrrocinia (27). The majority of isolates identified as B. cepacia (85%), B. cenocepacia (90%), and B. ambifaria (76%) were pathogenic in a detached onion bulb scale assay and caused symptoms of water soaking, maceration, and/or necrosis.

This study confirmed that multiple B. cepacia complex species colonize the onion rhizosphere and have the potential to cause sour skin rot disease of the onion. In addition, the onion rhizosphere is a natural habitat and a potential environmental source of B. cenocepacia. Following the introduction of segregation of patients growing B. cepacia most new infections were with such environmentally acquired organisms.

A review of the current recommendations for timing of lung transplantation in individuals with end-stage cystic fibrosis lung disease and on the rationale behind listing decisions. Guidelines for the referral and selection of patients suitable for lung transplantation were recently updated by the pulmonary council of the International Society for Heart and Lung Transplantation. However, an analysis published in 2007 has questioned whether lung transplantation extends life in children with cystic fibrosis. There are some concerns regarding this analysis, and these are discussed in detail. Most importantly, the analysis is specific to the United States and predates the introduction of the lung allocation score, which has had a marked impact on how transplant organs are allocated in this country. It is likely that lung transplantation can extend life in both adults and children with cystic fibrosis, provided the procedure is correctly timed. Further development of the lung allocation score has the potential to increase the survival benefit from the procedure in the United States.

Paul Aurora, consultant respiratory paediatrician at Great Ormond Street Hospital London, defended the benefit derived by children from lung transplantation in a number of publications and supports the view that both children and adults benefit from the procedure - it having been suggested from the USA that children failed to benefit. He has had extensive experience in supervising the UK paediatric transplant service at Great Ormond Street Hospital, London.

Determination of chloride concentration in sweat is the current diagnostic gold standard for CF. Nanoduct is a new analyzing system measuring conductivity which requires only 3 microliters of sweat and gives results within 30 minutes. The authors concluded that the Nanoduct test is a reliable diagnostic tool for CF diagnosis: It has a failure rate comparable to other sweat tests and can be used as a simple bedside test for fast and reliable exclusion, diagnosis or suspicion of CF.
In cases with borderline conductivity (60–80 mmol/L) other additional methods (determination of chloride and genotyping) are indicated.

In the past rapid methods of sweat testing, such as the chloride electrode have proved unreliable. This method does seem to be a more reliable method. Always the remembering the potential for disastrous diagnostic mistakes which can occur as a result of unreliable sweat tests.

The treatment group was supplemented with algal DHA-rich oil and the control group with sunflower seed oil. There was no difference between the control and treatment groups for W/H%, caloric intake, FEV1% and FVC% at the start of the study and after 1 year of supplements.

So although DHA-rich oil shifted the serum phospholipid fatty acids to a less pro-inflammatory profile, no conclusive clinical improvement could be observed.

Anaerobic species were isolated 64% of sputum samples from adult patients with CF. Similar anaerobic species were identified in bronchiolar lavage fluid from pediatric patients with CF.
Although anaerobes were detected in induced sputum samples from 16 of 20 volunteers, they were present in much lower numbers and were generally different species compared with those detected in CF sputum. All isolates were susceptible to meropenem.
So a range of anaerobic species are present in large numbers in the lungs of patients with CF. If these anaerobic bacteria are contributing significantly to infection and inflammation in the CF lung, informed alterations to antibiotic treatment to target anaerobes, in addition to the primary infecting pathogens, may improve management.

Over the years there have been sporadic reports of anaerobes in the sputum of people with CF (Jeeves & Spencer. J Med Microbiol 1990; 31:271-274. [PubMed]
As yet there is no definite information as to their importance. Their presence in induced sputum specimens of 16 of 20 volunteers is rather confusing even though their numbers were less than in the CF patients.

Intravenous continuous infusion of betalactam (CIBL) antibiotic and high dose extended interval (HDEI) aminoglycoside therapy theoretically maximize bacterial killing in treatment of Pseudomonas aeruginosa in pulmonary exacerbations of cystic fibrosis (CF). A 3-month-old female infant with CF failed outpatient eradication of Pseudomonas with subsequent eradication using intravenous CIBL antibiotic and HDEI aminoglycoside therapy. This antibiotic combination should be considered in order to optimize pharmacodynamics for Pseudomonas eradication in CF patients before development of chronic colonization.

An important case report from Kentucky of an aggressive and successful eradication of P aeruginosa not accepting failure. The use of continuous IV beta lactam (eventually aztreonam here) and intermittent high dose IV tobramycin would be worth further investigation. The fact that failed eradication is receiving attention from a centre in the USA is encouraging and indicates a new approach. It is important to leave no stone unturned when attempting to eradicate P. aeruginosa; this often involves giving intravenous antibiotics to small children with CF who do not appear unwell. In these circumstances it would seem sensible to use the antibiotics in the optimal way as in this report.

Written infection control policies used at CF care sites in the United States were compared with recently published guidelines (Saiman et al, 2003). Most policies recommended contact precautions for hospitalized patients infected with Burkholderia cepacia complex (73%), multidrug-resistant organisms (63%), and methicillin-resistant Staphylococcus aureus (64%). Socializing among CF patients was discouraged in 80% of inpatient policies and 55% of outpatient policies. Although routine mask use by patients remains an unresolved issue, many policies advocated this practice. Future studies should address barriers to implementation of these evidence-based guidelines and continue to monitor implementation.

That contact precautions were only recommended in 73% of centres even with B. cepacia is rather surprising one would have expected 100%. Permitting contact between people with B. cepacia in a CF centre would raise serious issues in the UK.

This study aimed to establish the degree of transmission resulting in subsequent infection of P. aeruginosa among 80 children with CF attending holiday camps in The Netherlands. The study was...
performed in the summer of 2001 in four camps organised simultaneously at different locations. Sputum was collected on day 1 of the holiday, and three and six months later. Different morphotypes of *P. aeruginosa* from sputum were genotyped by AFLP analysis. Criteria were defined for the degree of evidence of transmission. There were 18 cases of possible, 2 cases of “probable” transmission and 1 case of “highly probable” transmission. Two predominant types of *P. aeruginosa* were found (types 18 and 23). Type 18 was already prevalent on day 1 mostly in younger children and was involved in eleven cases of transmission; type 23 was involved in six cases of transmission among older children.

There was a considerable risk of transmission of *P. aeruginosa* during these holiday camps for children with CF in The Netherlands. Two genotypes of *P. aeruginosa* appeared to be easily transmissible, one of which seemed common in the Dutch CF population. Previous work from the Netherlands had shown little evidence of cross infection at camps and at the time the professionals involved considered the benefits of the holidays outweighed the risks of infection. For example in 1995 Hoogkamp-Korstanje et al (J Clin Microbiol 1995; 33:572-575. [PubMed]) considered the risk was comparable with that observed in the community. "We conclude that the risk of cross infection is trivial compared with the obvious joy and social benefit derived from a holiday camp". It is interesting how many years elapsed before these findings were published - holiday in 2001 and publication in 2008. A similar long interval occurred in the paper from Copenhagen (Ojyeniyi et al, 2000. [PubMed] when the study in 1990 was reported in 2000. [PubMed]


This double-blind, randomized, placebo-controlled Phase 2 study evaluated the safety, tolerability and efficacy of 75 mg and 225 mg aztreonam lysine (AZLI) administered twice daily for 14 days. There was a statistically significant reduction, compared to placebo, in *P. aeruginosa* CFU density in each AZLI group at Days 7 and 14 (P<0.001). The planned primary analysis, percent change in FEV1 at Day 14, demonstrated no statistically significant difference. Further analysis demonstrated significant increase in FEV1 at Day 7 for the subset of patients with baseline FEV1<75% predicted in the 225 mg AZLI group. Bronchodilator use was associated with greater improvement in FEV1, as well as greater reduction in *P. aeruginosa* bacterial density and higher plasma aztreonam concentrations in the 225 mg AZLI group. The authors concluded that these data support the further development of AZLI and provide information for the design of subsequent studies (Retsch-Bogart et al, 2008 below).


Phase III study of treatment with 28 days of AZLI 75mg three times daily led to significant improvements in FEV1 and FVC compared to controls. At 28 days treated group had 10.2 better FEV1% and 5 better FVC% than did controls.

So inhaled aztreonam lysine is a valuable addition to the inhaled antibiotics available for treating people with CF and was licensed by 2010.


The CFTR mutation, which causes cystic fibrosis (CF), has also recently been identified as causing glutathione system dysfunction and systemic deficiency of reduced glutathione (GSH). Such dysfunction and deficiency regarding GSH may contribute to the pathophysiology of CF. Thirteen patients (age range 1-27 years) with CF who were using a regimen of reduced glutathione (GSH), including oral glutathione and inhaled buffered glutathione in an uncontrolled study, were followed in an observational study. Dosage ranged from 66-148 mg/kg/day in divided doses, and the term examined was the initial 5.5 months of GSH use (45 days of incrementally adjusted dose, plus 4 months of use at full dosage). Significant improvement in the following clinical parameters was observed: average improvement in FEV1 percent predicted (N=10) was 5.8 percentage points (p<0.0001), average weight percentile (N=13) increased 8.6 points (p<0.001), BMI percentile (N=11) improved on average 1.22 points (p<0.001). Positive sputum cultures of bacteria in 11 patients declined from 13 to 5 (p<0.03) with sputum cultures of Pseudomonas aeruginosa becoming negative in 4 of 5 patients previously culturing PA, including two of three patients chronically infected with PA as determined by antibody status. Use of a daily GSH regimen appears to be associated in CF patients with significant improvement in lung function and weight, and a significant decline in bacteria cultured in this uncontrolled study.

The authors of this study are convinced as to the value of glutathione and considered these findings warrant further clinical investigation in larger, randomized, controlled studies as has been suggested by protagonists of the use of glutathione Clark Bishop and Valerie Hudson. (Bishop et al, 2005 above for more detail).

As part of Dr Claire Wainwright’s study of bronchoalveolar lavage (BAL) directed therapy, 333 BALs were carried out on 107 children median age 23.5 months (1.6 - 67.5 months); 170 (51%) were for exacerbations. 8.7% were followed by fever and 3% clinically significant episodes. 52% had minor adverse events. The authors concluded that although adverse events were common they were usually transient and well tolerated. Parents should be warned that infants with respiratory infections had an increased risk of post-BAL fever.

This is an important ongoing study further progress of which was reported by Claire Wainwright (figure 57.2) at the 2009 NACFC in Minneapolis. The study concluded in 2009 and although was a source of vast and important information, did not establish a case of managing the respiratory infections using regular bronchoscopies - undoubtedly one of the major studies of the decade!

Claire Wainwright is a paediatric respiratory physician and head of CF services at the Royal Children’s Hospital, Brisbane, Australia. She started her medical and paediatric training in London and completed her training in paediatric respiratory medicine and doctoral studies at the Royal Children’s Hospitals in Brisbane and Melbourne. Her research interests include early lung disease, airway microbiology, metabolic problems and patient-reported outcomes in CF, and management of bronchiolitis and asthma.

Fig 57.2. Prof Claire Wainwright

This supplement offers detailed consensus guidelines based on review of the literature and experience of paediatricians, adult and transplant physicians, and nurses, physiotherapists, dietitians, pharmacists and psychologists experienced in CF and anaesthetists and obstetricians with experience of CF pregnancy.


This study aimed to provide expert consensus regarding the physiotherapy management of asymptomatic infants with CF using a Delphi consensus method. Twenty-five senior paediatric physiotherapists from Specialist CF Centres throughout the UK participated in the study. Consensus was high but consensus could not be achieved on whether routine daily chest physiotherapy is necessary in 'asymptomatic' babies. An agreed amendment to the original statement allows professionals to modify or change traditional practice with the sanction of their senior colleagues. There had been a considerable amount of discussion as to the practice of tipping infants in the head down position which Brenda Button and her colleagues from Melbourne found caused oesophageal reflux in a significant proportion.


The diagnosis of infants detected by neonatal CF screening is not always straightforward and this report gives advice to employ a combination of clinical presentation, laboratory testing and genetics to confirm a diagnosis of CF. A European CF Society consensus report also dealt with problem of equivocal diagnosis after neonatal CF screening and dealt with sweat testing, further assessment and investigations, review arrangements and the database (Mayell SJ et al. J Cyst Fibros 2009; 8:71-78. [PubMed]


The aim of our study is to evaluate the association between CFTR gene mutations with asthma and pulmonary function abnormalities. For this purpose, 214 mutation carriers were compared to 185 non-carriers. Although the relative risk of asthma did not differ between groups (OR=0.61, 95% CI: 0.23-1.61, p=0.32), the values of FEV1, and FEV1/FVC ratio were lower in carriers (p=0.001, and p<0.001, respectively). This may imply that heterozygosity may be related with a silent obstructive pulmonary profile.
The objective of this study was to describe our experience in which rhDNase (Pulmozyme) was administered by bronchoscopic instillation into atelectatic lobes in five adults with CF. This method was successful in treating lobar atelectasis, which was resistant to conventional therapy with antibiotics and physiotherapy. In all but one of the cases we described, administration of DNase in this manner resulted in a radiographic and clinical improvement of the atelectasis. We recommend that respiratory physicians consider this as a second line treatment in the management of atelectasis.

Although not the first to use this treatment for atelectasis, confirmation of the success of this treatment is useful for clinicians faced with resistant atelectasis.

In some cases, cystic fibrosis may include intestinal inflammation and bacterial overgrowth. Probiotics are considered as immunomodulatory, anti-inflammatory and microbiotic regulator substances. The aim of our study is to determine the prevalence of bacterial overgrowth in cystic fibrosis patients and try to improve the intestinal function with the administration of probiotics. We examined 20 patients with cystic fibrosis (mean age 10.33, range 5 to 17 years). The expired hydrogen test with a 2 g/kg of 20% dextrose overload was performed on 10 patients. After the test, Lactobacillus rhamnosus LGG 10(11) CFU was administered twice daily for four weeks. Faecal near infrared spectroscopy (FENIR) of water, fat, nitrogen and sugar content in faeces was performed before and after probiotics administration. Five patients (50%) showed bacterial overgrowth. We obtained a positive correlation between the hydrogen test and steatorrhoea (R = 0.57) and sugar in faeces (R = 0.52). The FENIR results pre-treatment vs post-treatment were: fat 6.2 g +/- 3.3 g vs. 4.9 g +/- 2.1 g (p < 0.05), sugar 6.7 g +/- 3.6 g vs. 5 g +/- 2.6 g (p < 0.05) and nitrogen 0.87 g +/- 0.27 g vs. 0.91 g +/- 0.14 g (NS) respectively. Thirteen patients (81.25%) had improved stool appearance and intestinal comfort and nine (56.25%) decreased the number of daily stools. Probiotics improved not only clinical but also biochemical intestinal function in cystic fibrosis patients. These could be given as a regular treatment in this type of patients and in those with bacterial overgrowth.

One of the few papers on the use of probiotics in people with CF. With the increasing evidence of bacterial overgrowth and tissue inflammation it is likely that probiotics may have a role in treatment of gastrointestinal problems.

This study investigated the PFGE genetic pattern and antimicrobial resistance profile of 42 A. xylosoxidans isolates obtained over 4 years from the respiratory tract of 22 CF patients. The majority of the isolates showed multi drug resistance; imipenem and piperacillin were the most active drugs. During the course of A. xylosoxidans chronic infection forced expiratory volume and body mass index values were not significantly lowered. Our data suggest that in some cases the infection may have been acquired from other patients or from a common contaminated source. Further epidemiological studies may be important for the design and implementation of prophylactic measures in CF centers.

This study looks at the use of inhaled steroids from another angle to that of Ian Balfour- Lynn. These results could have been predicted and support previous knowledge of inhaled steroids. The growth effect is of course dependant on the dose used - sometimes the heroic doses

Another emerging pathogen for people with CF.
used for various drugs for children with CF have serious side effects - one has seen growth totally arrested by very large doses of inhaled steroids in a small child with CF. The study leaves the paediatrician to decide in the case of individual patients if inhaled steroids are indicated. It is clear that there are some children who do benefit from inhaled corticosteroid treatment.


Since 1989, CF-patients intermittently colonized with Pseudomonas aeruginosa have been treated with inhaled colistin and oral ciprofloxacin in the Copenhagen CF-centre. The study evaluates 15 years results of this treatment. METHODS: All isolates of P. aeruginosa from CF-patients intermittently colonized with P. aeruginosa from 1989 to 2003 were identified. All anti-P. aeruginosa treatments were evaluated for antibiotics used, treatment duration, pseudomonas-free interval and development of chronic infection. All P. aeruginosa isolates were assessed for resistance and for non-mucoid or mucoid phenotype. RESULTS: 146 CF-patients were included in the study (1106 patient-years). 99 patients had first ever isolate during the study period. Median observation time 7 years (0.1-14.9). 12 patients developed chronic infection. A Kaplan Meyer plot showed protection from chronic infection in up to 80% of patients for up to 15 years. 613 colistin/ciprofloxacin treatments were given. There was no difference in pseudomonas-free interval comparing 3 weeks (5 months) and 3 months (10.4 months) of colistin and ciprofloxacin, but a significant difference compared to no treatment (1.9 months). Patients developing chronic infection had significantly shorter pseudomonas-free interval after treatment of first ever isolate compared to patients remaining intermittently colonized (p<0.003). Treatment failure (P. aeruginosa-positive culture immediately after ended treatment of first ever isolate) was a strong risk factor for development of chronic infection after 3-4 years, OR 5.8. 1093 pseudomonas-isolates were evaluated (86.6% non-mucoid). No colistin-resistance was found. Ciprofloxacin-resistance was found in 4% of isolates. CONCLUSION: Treatment of intermittent P. aeruginosa colonization in CF-patients using colistin and ciprofloxacin can protect up to 80% of patients from development of chronic infection for up to 15 years. A positive culture immediately after treatment of first ever isolate is a strong risk factor for development of chronic infection. We found no colistin-resistance and minimal ciprofloxacin-resistance.

This valuable experience from the team in Copenhagen is reported in full as it represents experience from one of the first European CF centres to introduce early eradication therapy for P. aeruginosa. The effect of this treatment has protected many patients from chronic P. aeruginosa infection for many years. There was some resistance as reported in Johansen et al 2008 [PubMed] but this was not a major problem.


Colistin resistant Pseudomonas aeruginosa have rarely been reported in cystic fibrosis (CF) patients. We performed a 17-year prospective study on colistin susceptibility and compared our findings with clinical variables. The first outbreak started in 1995 and lasted 5 years. It involved 27 CF patients who had inhaled colistin twice daily for a median of 10 years. Colistin resistant isolates persisted in individual patients for a median of 75 days after colistin was withdrawn. A second outbreak started in 2004. It involved 40 patients, 17 of whom were the same as in the first outbreak. Most resistant isolates belonged to two major clones that had similar genotypes in the two outbreaks. The P. aeruginosa isolates were all non-mucoid and they appeared in a group of chronically infected patients that had been admitted to the same ward for antibiotic treatment and had been followed at the same week-days in the outpatient clinic. Patients were individually isolated to avoid cross-infection and colistin inhalation was avoided in the CF outpatient clinic and in the ward after both outbreaks. Since 2004, no further spread has been observed. It is important that the colistin resistant clones do not spread to non-infected patients since colistin is an important antibiotic for eradication of initial and intermittent P. aeruginosa colonisation.

Infrequent resistance even with widespread use of colistin in the Danish CF centre


79 patients with CFRD were matched with 79 patients with DM1 according to sex, age and duration of insulin therapy. Retinopathy, peripheral neuropathy, nephropathy and microalbuminuria were the microvascular complications assessed. Risk factors studied were: smoking, BMI, HbA1c, cholesterol, cholesterol/HDL ratio, diastolic and systolic blood pressure. Both groups had the same number of microvascular complications (29%). CFRD patients showed more microalbuminuria (21% versus 4.1%; p = 0.003), while retinopathy was more common in patients with DM1 (24% versus 10%; p = 0.044). The prevalence of peripheral neuropathy and nephropathy were similar. Patients with CFRD had lower BMI (p<0.0001), total cholesterol (p<0.0001) and Hba1c (p = 0.056) levels, and a lower prevalence of smokers (p<0.0001). Cholesterol/HDL ratio and diastolic and systolic blood pressure were similar in both groups. The microvascular complications shown by patients with CFRD are similar to those seen in patients with DM1 but with a lower prevalence of retinopathy and a higher prevalence of microalbuminuria. The latter may reflect the influence of other cystic fibrosis-related factors on renal function.

Three cases of Clostridium difficile pancolitis in adults with cystic fibrosis (CF) in whom the presenting symptoms were atypical. All three required treatment with systemic steroids, in addition to oral vancomycin and metronidazole to achieve resolution of the colitis. This experience suggests that C. difficile colitis should be considered in individuals with CF presenting with non-specific abdominal symptoms.

There have been sporadic reports of C difficile infection in people with CF. Some have been in patients who have had lung transplants. Also asymptomatic carriage seems to be relatively common in CF. In a minority the infection leads to serious clinical illness as in the cases reported here.


It is not routine practice to advise on seating position within the car in relationship to the seatbelt placement over the anterior chest wall. Line failure due to direct pressure from a seatbelt worn to prevent injury in the sudden deceleration involved during a motor vehicle accident (MVA) has not been described previously in the CF literature We report the case of an 8 year old child who fractured her Vascuport(R) line secondary to seatbelt trauma following a road traffic accident (RTA). Children and adults with CF should be advised to sit in the car on the side that places the shoulder strap of the seatbelt on the opposite side to the TIVAD line.

This is a useful practical report which will help to prevent a complication not previously reported.


In CF patients, the prevalence of rheumatic symptoms increases with age and CF severity. Our data suggest an association of infections with P. aeruginosa and A. fumigatus with the occurrence of rheumatic symptoms. However, no association of CF with definite inflammatory joint or connective tissue diseases was observed, and no CF-specific pattern of musculoskeletal symptoms was seen.

We did report a definite association between the severity of the joint pains and severity of the chest infection as they definitely improved during a course of intravenous antibiotics (Bowler IM, Littlewood JM. Episodic arthritis in cystic fibrosis. lancet 1992; 340:244. [PubMed]


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Cystic fibrosis affects all secretory epithelia, including the eye, and belongs to the group of ocular surface epithelial diseases, termed keratoconjunctivitis sicca or dry eye syndrome. The aim of this study was to evaluate goblet cell population and conjunctival epithelial morphology in patients with CF. A total of 20 CF patients and 20 controls underwent conjunctival impression cytology. Impression cytology showed conjunctival squamous metaplasia and goblet cell loss in patients with CF. The reduced goblet cell numbers and squamous metaplasia may be indicative of a higher degree of epithelial damage of conjunctival epithelial cells in CF patients, and the presence of neutrophils is a strong sign for an inflammatory background of this disease. In view of the simple, noninvasive nature of impression cytology, this technique may prove to be an important tool for the diagnosis and monitoring of dry eye changes in CF patients.

These changes are reported in a number of reports dealing with vitamin A status and still appear to be present even when the vitamin levels are normal. (Ansari EA et al. 1999) [PubMed] to the extent that it has been suggested that dry eye could be a primary manifestation of CF.


In about 10% of patients worldwide and more than 50% of patients in Israel, cystic fibrosis results from nonsense mutations (premature stop codons) in the messenger RNA (mRNA) for the cystic fibrosis transmembrane conductance regulator (CFTR). PTC124 is an orally bioavailable small molecule that is designed to induce ribosomes to selectively read through premature stop codons during mRNA translation, to produce functional CFTR: This phase II prospective trial recruited adults with cystic fibrosis who had at least one nonsense mutation in the CFTR gene. Patients were assessed in two 28-day cycles. During the first cycle, patients received PTC124 at 16 mg/kg per day in three doses every day for 14 days, followed by 14 days without treatment; in the second cycle, patients received 40 mg/kg of PTC124 in three doses every day for 14 days, followed by 14 days without treatment. The primary outcome had three components: change in CFTR-mediated total chloride transport; proportion of patients who responded to treatment; and normalisation of chloride transport, as assessed by transepithelial nasal potential difference (PD) at baseline, at the end of each 14-day treatment course, and after 14 days without treatment. Transepithelial nasal
PD was evaluated in 23 patients in the first cycle and in 21 patients in the second cycle. Mean total chloride transport increased in the first treatment phase, with a change of -7.1 (SD 7.0) mV (p<0.0001), and in the second, with a change of -3.7 (SD 7.3) mV (p=0.032). We recorded a response in total chloride transport (defined as a change in nasal PD of -5 mV or more) in 16 of the 23 patients in the first cycle's treatment phase (p<0.0001) and in eight of the 21 patients in the second cycle (p<0.0001). Total chloride transport entered the normal range for 13 of 23 patients if the first cycle's treatment phase (p=0.0003) and for nine of 21 in the second cycle (p=0.02). Two patients given PTC124 had constipation without intestinal obstruction, and four had mild dysuria. No drug-related serious adverse events were recorded. In patients with cystic fibrosis who have a premature stop codon in the CFTR gene, oral administration of PTC124 to suppress nonsense mutations reduces the epithelial electrophysiological abnormalities caused by CFTR dysfunction.


Chronic infection with Pseudomonas aeruginosa is common in cystic fibrosis (CF) and certain strains are more transmissible and virulent than others. Of these, the Liverpool Epidemic Strain (LES) is highly transmissible and cross infection has been reported between patients with CF and healthy non-CF relatives. However, the risk of transmission from humans to animals is unknown. The first report of interspecies transmission of the LES strain of P. aeruginosa from an adult patient with CF to a pet cat is described. This development further complicates the issue of infection control policies required to prevent the spread of this organism.


In an open crossover study of CF patients, subjects were randomly allocated to receive either 80 mg tobramycin twice-daily continuous treatment or 300 mg tobramycin twice daily in cycles of 28 days on and 28 days off treatment. After three months, patients were switched to the alternative treatment regimen. A total of 32 patients with a mean (+/- SD) age of 18.5+/-.8.6 years were included in the study. Compared with the treatment period using colistin, forced expiratory volume in 1 s decreased by -2.1+/-.13.8% in the 80 mg tobramycin group and increased by +2.3+/-.13.0% in the 300 mg group. Similar changes were observed in forced vital capacity (-2.5+/-.12.9% in the 80 mg tobramycin group versus +2.5+/-.9.6% in the 300 mg tobramycin group). Variability in responses was large but the differences were not statistically significant. Personal preference indicated that the majority of patients preferred the high-dose cycle compared with the lower dose continuous inhalation, but this was not linked to objective data on efficacy. The present trial fails to provide convincing evidence for superiority in efficacy of either of the two treatment regimens of inhaled tobramycin in CF patients.

In the UK since the Eighties injectable tobramycin was nebulised by people with CF to suppress their chronic P aeruginosa chest infection. It is disappointing that the results in this trial were inconclusive although the dose difference appeared to tip the balance in favour of the TOBI. Tobramycin injectable is no longer licensed for inhalation in the UK.


176 patients with CF underwent lung transplantation at the Freeman Hospital Newcastle UK. The majority (168) had bilateral sequential lung transplantation. Median age at transplantation was 26 years. Diabetes was common pretransplantation (40%). Polymicrobial infection was common in individual recipients. A diverse range of pathogens were encountered, including the Burkholderia cepacia complex (BCC). The bronchial anastomotic complication rate was 2%. Pulmonary function (FEV1 % predicted) improved from a pretransplantation median of 0.8 l (21% predicted) to 2.95 l (78% predicted) at 1 year following transplantation. We noted an acute rejection rate of 41% within the first month. Our survival values were 82% survival at 1 year, 70% at 3 years, 62% at 5 years and 51% at 10 years. Patients with BCC infection had poorer outcomes and represented the majority of those who had a septic death. Data are from those free from these infections. Bronchiolitis obliterans syndrome (BOS) and sepsis were common causes of death. Freedom from BOS was 74% at 5 years and 38% at 10 years. Biochemical evidence of renal dysfunction was common although renal replacement was infrequently required (<5%). The authors concluded that lung transplantation is an important therapeutic option in patients with CF even in those with more complex microbiology. Good functional outcomes are noted although transplantation associated morbidities accrue with time.

These excellent results are from the UKs largest transplant centre and the summary is reproduced in full.


Among the most promising of the new therapies being developed for the treatment of Cystic Fibrosis (CF) are those targeted at increasing mucosal hydration on the surface of the airways. One of these therapies, P2Y(2) receptor agonists, bypasses the defective CFTR chloride channel, and activates an alternative chloride channel. This activation results in an increase in airway
surface epithelial hydration, and through these actions and effects on cilia beat frequency, increases mucociliary clearance. The pharmacology of P2Y(2) agonists has been confirmed in several preclinical and clinical studies. Denufosol tetrasodium is a novel second-generation, metabolically stable, selective P2Y(2) receptor agonist currently in Phase 3 clinical development. In radio labelled deposition studies of P2Y(2) agonists in healthy non-smokers and smokers, approximately 7mg of a 40-mg nebulizer (PARI LC Star) load was deposited in the lungs. In a pharmacokinetic study in healthy volunteers, very limited systemic exposure was observed when doses of 200mg of denufosol were nebulized. Thus, it appears that high concentrations of denufosol can be achieved in the airways with very low systemic absorption. Denufosol has been generally well-tolerated in healthy volunteers and patients with CF. The most commonly reported adverse events were in the respiratory system, with cough having the highest frequency. Doses of 20-60mg have been evaluated in Phase 2 trials of up to 28 days duration, and superiority relative to placebo on FEV1 has been observed in patients with relatively normal lung function (FEV1 greater than or equal to 75% of predicted). The first Phase 3 trial is a comparison of denufosol 60mg and placebo in 350 patients with CF with FEV1 at study entry greater than or equal to 75% of predicted.

One of the more hopeful new therapies with the particular aim of increasing hydration of the mucosa.


RG. Robertson CF. Bye PT. Lesouëf PN. Shadbolt B. Anderson SD. Charlton B. Inhaled mannitol improves lung function in cystic fibrosis. Chest 2008; 133:1388-1396. [PubMed]. Inhaled mannitol is an osmotic agent that increases the water content of the airway surface liquid, and improves the clearance of mucus with the potential to improve lung function and respiratory health. To this end, this study examined the efficacy and safety of therapy with inhaled mannitol over a 2-week period in a randomized, double-blind, placebo-controlled, crossover study. Thirty-nine subjects with mild-to-moderate CF lung disease inhaled 420 mg of mannitol or placebo twice daily for 2 weeks. Following a 2-week washout period, subjects were entered in the reciprocal treatment arm. Lung function, respiratory symptoms, quality of life, and safety were assessed. Mannitol treatment increased FEV(1) from baseline by a mean of 7.0% (95% confidence interval [CI], 3.3 to 10.7) compared to placebo 0.3% (95% CI, -3.4 to 4.0; p < 0.001). The absolute improvement with mannitol therapy was 121 mL (95% CI, 56.3 to 185.7), which was significantly more than that with placebo (0 mL; 95% CI, -64.7 to 64.7). The forced expiratory flow in the middle half of the FVC increased by 15.5% (95% CI, -6.5 to 24.6) compared to that with placebo (increase, 0.7%; 95% CI, -8.3 to 9.7; p < 0.02). The safety profile of mannitol was adequate, and no serious adverse events related to treatment were observed. Inhaled mannitol treatment over a period of 2 weeks significantly improved lung function in patients with CF.

Mannitol therapy was safe and well tolerated.

Mannitol was developed further and licensed in 2010. 2008 Smyth A. Lewis S. Bertenshaw C. Choonara I. McGaw J. Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2008; 63:532-535. [PubMed]. There has been a recent increase in the number of reported cases of acute renal failure (ARF) in cystic fibrosis (CF). A case-control study was conducted to determine the factors which are associated with an increased risk of ARF. METHODS: 24 cases of confirmed ARF were identified in patients with CF from 20 UK CF centres presenting between 1997 and 2004. Using the UK CF database, sex- and age-matched controls were identified. Risk factors were analysed by conditional logistic regression and Mantel-Haenszel analysis. RESULTS: 21 of the 24 patients with ARF had received an aminoglycoside at the time of their episode of ARF or in the preceding week compared with only 3 of 42 controls during the same time period (OR 81.8, 95% CI 4.7 to 1427, p<0.001). In the year before the episode of ARF, significantly more cases than controls had received gentamicin (19/24 cases vs 1/42 controls, p<0.001). The numbers receiving tobramycin were similar (9/24 cases vs 16/42 controls, p = 0.9). A known risk factor for renal impairment (prior renal disease, acute dehydration or long-term treatment with a nephrotoxic drug) was present in 18/24 cases and 7/42 controls (OR 24.0, 95% CI 3.1 to 186.6, p = 0.002). CONCLUSIONS: In patients with CF the use of an intravenous aminoglycoside is a risk factor for ARF; gentamicin is more nephrotoxic than tobramycin. Most patients who develop ARF have a risk factor which necessitates withholding an aminoglycoside or more closely monitoring their use.

An important paper from Alan Smyth confirming the increase in severe renal problems in people with CF. The immediate lesson being that gentamicin should not be used in people with CF who require repeated courses of intravenous aminoglycosides.


Interaction with plants around their roots and foliage forms the natural habitat for a wide range of bacteria: opportunistic pathogens with important natural biology. J App Microbiol 2008; 104:1539-1551. [PubMed]. The B. cepacia complex is composed of nine formally named species groups and several preclinical and clinical studies. Denufosol tetrasodium is a novel second-generation, metabolically stable, selective P2Y(2) receptor agonist currently in Phase 3 clinical development. In radio labelled deposition studies of P2Y(2) agonists in healthy non-smokers and smokers, approximately 7mg of a 40-mg nebulizer (PARI LC Star) load was deposited in the lungs. In a pharmacokinetic study in healthy volunteers, very limited systemic exposure was observed when doses of 200mg of denufosol were nebulized. Thus, it appears that high concentrations of denufosol can be achieved in the airways with very low systemic absorption. Denufosol has been generally well-tolerated in healthy volunteers and patients with CF. The most commonly reported adverse events were in the respiratory system, with cough having the highest frequency. Doses of 20-60mg have been evaluated in Phase 2 trials of up to 28 days duration, and superiority relative to placebo on FEV1 has been observed in patients with relatively normal lung function (FEV1 greater than or equal to 75% of predicted). The first Phase 3 trial is a comparison of denufosol 60mg and placebo in 350 patients with CF with FEV1 at study entry greater than or equal to 75% of predicted.

One of the more hopeful new therapies with the particular aim of increasing hydration of the mucosa.

which are all difficult to identify using phenotypic methods. Genetic methods such as 16S rRNA and recA gene sequence analysis have proven useful for Bcc species identification. Multilocus sequence typing (MLST) is also emerging as a very useful tool for both Bcc strain and species identification. Historically, Burkholderia cepacia was the most dominant Bcc pathogen in CF, however, probably as a result of strict infection control practices introduced to control the spread of this species, its prevalence has been reduced. Burkholderia multivorans is the now the most dominant Bcc infection encountered in the UK CF population, a changing epidemiology that also appears to be occurring in the US CF population. The distribution of Bcc species residing in the natural environment may vary considerably with the type of environment examined. Clonally identical Bcc strains have been found to occur in the natural environment and cause infection. The contamination of medical devices, disinfectants and pharmaceutical formulations has also been directly linked to several outbreaks of infection. In the last 10 years considerable progress has been made in understanding the natural biology and clinical infections caused by this fascinating group of bacteria.

An up to date review of the B. cepacia complex by Esch Malenthiralingam, an expert on the subject of BC complex. The summary is reproduced in full.


It is often challenging for the clinician interested in cystic fibrosis (CF) to interpret molecular genetic results, and to integrate them in the diagnostic process. The limitations of genotyping technology, the choice of mutations to be tested, and the clinical context in which the test is administered can all influence how genetic information is interpreted. This paper describes the conclusions of a consensus conference to address the use and interpretation of CF mutation analysis in clinical settings.

This is a major review by an international group of experts of the best way to use mutation analysis in cystic fibrosis.


The present study was conducted to portray the spectrum of hygienic measures and to evaluate the restrictions and impact caused by these measures. : In a multi-centre survey, parents of children below 13 years of age responded to mailed questionnaires. The items covered parental knowledge of PA, information provided by caregivers, the parents' feelings and thoughts about PA infection, and measures taken in daily life to prevent a possible contact with PA in the environment. 130 parents from 10 CF centres responded to the questionnaire (63% response rate). 76% of the respective children had always been PA negative. Most parents displayed erroneous beliefs regarding PA infection (mean: 3.5 correct replies to 9 questions). Families performed a mean of 11 different hygienic measures, e.g. they prevented their child from being the first person to use the bathroom in the morning (72%) or from bathing in gravel pits and standing water (52%). The majority of parents felt markedly (44%) or somewhat (44%) stressed that their child might acquire PA, and many parents felt markedly (16%) or somewhat (43%) restricted and stressed by the hygienic measures. Less stressed parents tended to have more knowledge and undertook fewer measures. When informing and teaching parents on the nature of PA infection, caregivers should provide clear recommendations on reasonable actions to be taken. Also, physicians should anticipate and adequately respond to parental fears and misconceptions.

This was a useful study looking at the difficult question of just what precautions do parents take to avoid exposing their CF child to situations likely to pose a high risk of infection, particularly with P. aeruginosa whilst still maintaining as normal a life style as possible.


The objective of this study from Brisbane was to determine if hepatic ultrasound findings in paediatric patients with cystic fibrosis and suspected liver disease are related to histopathological results derived from liver biopsies. The authors concluded that the diagnosis of early liver disease in cystic fibrosis cannot reliably be made on the basis of ultrasound alone. A normal ultrasound does not preclude significant liver fibrosis in cystic fibrosis. An abnormal US that suggests cirrhosis predicts the presence of moderate to severe liver disease.


To evaluate and compare the clinical outcomes of children with cystic fibrosis (CF) managed primarily at a tertiary cystic fibrosis centre (CFC) with those treated at regional centres by local health care professionals and the cystic fibrosis outreach service (CFOS). A retrospective study of 273 children with CF born between 19 October 1982 and 19 February 2002 and with clinical data available between 1 January 2000 and 31 December 2002. Patients were grouped into CFC (n = 131) or CFOS (n = 142), with CFOS then further categorized into three groups depending on the
level of care they received. There were no significant differences in pulmonary function, P. aeruginosa status, or height and weight z scores between children managed by CFC or by CFOS. Children receiving more care at the CFC (level of care [LOC] 1 and 2) were more likely to have multiple hospital admissions than children receiving more care in regional areas (LOC 3 and 4) (P < 0.001). The authors concluded the CFOS model provides effective delivery of specialised multidisciplinary care to children and adolescents living in rural and regional Queensland.

This is a reassuring study for the Australian families and professionals involved in this particular study. However, it is often difficult to translate the results of one study to another area or country.

The lung clearance index (LCI) from multiple-breath washout (MBW) is known to detect abnormal lung function more readily than spirometry in children and teenagers with CF, but its relationship to structural lung abnormalities is unknown. The authors concluded that LCI is a more sensitive indicator than FEV1 or FEF75 for detecting structural lung disease in CF, and a normal LCI almost excludes HRCT abnormalities. The finding of an abnormal LCI in some patients with normal HRCT scans suggests that LCI may be even more sensitive than HRCT scanning for detecting lung involvement in CF.

The lung clearance index is gaining increasing support as a measure of early non-invasive lung function also useful in young children. Interactions between secondhand smoke and genes that affect cystic fibrosis lung disease.

In cystic fibrosis (CF) patients, respiratory syncytial virus (RSV) infection is associated with significant morbidity. Although passive prophylaxis with palivizumab lowers hospitalization rate for RSV infection in populations at risk of severe infection, its use is not recommended in infants with CF disease. This study performed to determine the effect of palivizumab prophylaxis on hospitalization for acute respiratory illness in young children with CF during the first RSV season following the diagnosis of CF. A diagnosis of CF was made in 76 young children and data collected from 75 children. Of those, 40 did not receive RSV prophylaxis while 35 received palivizumab injection monthly during the RSV season. Among non-recipient children, 7 out of 40 were hospitalized for acute respiratory illness during the RSV season. Of these seven patients, RSV detection was positive in nasopharyngeal secretions in three patients, negative in one patient and not requested in the others. Among palivizumab recipients, 3 out of 35 children were hospitalized for acute respiratory illness during the RSV season. Of these seven patients, RSV detection was negative in nasopharyngeal secretions. Palivizumab recipients experienced fewer hospital days per patient for acute respiratory illness (mean +/- SD: 0.8 +/- 3.07 days) as compared to non-recipients (mean +/- SD: 1.73 +/- 4.27 days) but this difference did not reach statistical significance. The authors concluded that CF infants may benefit from RSV immunoprophylaxis with palivizumab.

RSV infection is a serious complication in young children with CF and may cause serious even fatal chest involvement.