THE NEW MILLENNIUM CLINICAL 2009


Nine patients with CF and ABPA (4 male, 5 female, ages 7-36 years) received HDIVPM (10-15 mg/kg/d), for 3 days per month, and itraconazole, until clinical and laboratory resolution of ABPA. All patients showed clinical and laboratory improvement (FEV1 increase, serum IgE levels and total eosinophil counts decrease) and treatment was discontinued after 6-10 pulses. Adverse effects were minor and disappeared shortly after each IV pulse therapy. The authors suggest that high-dose IV-pulse methylprednisolone is an effective treatment for ABPA in CF with minor side effects. This is a very useful report as the side effects of prolonged courses of oral corticosteroids (prednisolone) are often severe during treatment of ABPA - particularly the altered facial features.


A CF Foundation committee found no evidence that one method of airway clearance was superior to the others and although the evidence for benefit was not strong, recommended daily airway clearance be performed and regular exercise taken by all patients.

A number of studies have failed to show one method of airway clearance is significantly better than the others although other studies have confirmed that regular physiotherapy is definitely better than no physiotherapy. The Association of Chartered Physiotherapists in Cystic Fibrosis will publish their "Standards of Care and Good Clinical Practice for Physiotherapy Management of Children and Adults with Cystic Fibrosis" edited by Penney Argent, Lisa Morrison and Armani Prasad in 2011 which is an excellent review of the subject.


A subset (approximately 3%-5%) of patients with CF develops severe liver disease with portal hypertension. The objective of the study was to assess whether any of 9 polymorphisms in 5 candidate genes (alpha(1)-antitrypsin or alpha(1)-antiprotease [SERPINA1], angiotensin-converting enzyme [ACE], glutathione S-transferase [GSTP1], mannose-binding lectin 2 [MBL2], and transforming growth factor beta1 [TGFB1]) are associated with severe liver disease in patients with CF. The authors concluded that the SERPINA1 Z allele is a risk factor for liver disease in CF. Patients who carry the Z allele are at greater risk (OR, approximately 5) of developing severe liver disease with portal hypertension.


Patients with intermediate sweat chloride values in whom either additional CF diagnostic test was abnormal were compared with subjects in whom this was not the case and patients with classic CF. The phenotypic features of four groups were compared: 59 patients with CFTR dysfunction, 46 with an intermediate sweat chloride concentration but no evidence of CFTR dysfunction (CF unlikely), 103 patients with CF and pancreatic sufficiency (CF-PS) and 62 with CF and pancreatic insufficiency (CF-PI). The CFTR dysfunction group had more lower respiratory tract infections (p = 0.01), more isolation of CF pathogens (p<0.001) and clubbing (p = 0.001) than the CF unlikely group, but less frequent respiratory tract infections with CF pathogens than the CF-PS group (p = 0.05). Patients in the CF-PS group had a milder phenotype than those with PI. Many features showed stepwise changes through the patient groups. The authors concluded that patients with intermediate sweat chloride values and two CFTR mutations or an abnormal NPD measurement have a CF-like phenotype compatible with CFTR dysfunction and, as a group, differ phenotypically from patients with intermediate sweat chloride values in whom further CF diagnostic tests are normal as well as from CF-PS and CF-PI patients.

Although these conclusions seem obvious they are helpful when considering patients with a dubious diagnosis. Such patients should be referred to a CF Centre.
Miglustat (N-butyldeoxynojirimycin, Zavesca), an inhibitor of the alpha-1,2 glucosidase, has been proposed for clinical use in CF because of its effect as a corrector of the defective trafficking of F508del-CFTR. In the present study daily treatment for 2 months with low concentrations of miglustat on the human CF nasal epithelial cell line, JME/CF15 (F508del/F508del-CFTR), results in progressive, stable, reversible, and sustained correction of F508del-CFTR trafficking, down-regulation of sodium hyperabsorption, and regulation of the calcium homeostasis. These authors provide the first evidence that a respiratory CF cell can acquire a non-CF-like phenotype when chronically treated with low concentrations of a pharmacological drug.


Pseudomonas aeruginosa was isolated in cough aerosols of 25 subjects (89%), 22 of whom produced sputum samples. P aeruginosa from sputum and paired cough aerosols were indistinguishable by molecular typing. In four cases the same genotype was isolated from ambient room air. Approximately 70% of viable aerosols collected during voluntary coughing were of particles <or=3.3 micron aerodynamic diameter. P aeruginosa, Burkholderia cenocepacia, Stenotrophomonas maltophilia and Achromobacter xylosoxidans were cultivated from respiratory particles in this size range. Positive room air samples were associated with high total counts in cough aerosols (p = 0.003). The magnitude of cough aerosols was associated with higher forced expiratory volume in 1 s (r = 0.45, p = 0.02) and higher quantitative sputum culture results (r = 0.58, p = 0.008). The authors concluded that during coughing, patients with CF produce viable aerosols of P aeruginosa and other Gram-negative bacteria of respirable size range, suggesting the potential for airborne transmission.


Published studies concerning the impact of specialist care on lung disease in cystic fibrosis remain limited and most are either biased due to comparison with historical controls and/or underpowered. In this retrospective multicentric study, data from all CF children fulfilling the following criteria were collected: 1) Age 6yr and less than 18 yrs at the end of 2003; 2) diagnosed before 8 yrs; 3) follow-up in an accredited Belgian CF centre; 4) at least 1 spirometry and respiratory culture available for 2003. Group A included children referred 2 yrs or more after the diagnosis. Patients from Group A were then matched with a single early referred patient on the basis of 2 criteria: same centre, as closest age as possible (Group B). Data from 217 children were collected (Group A: 67). Late referred patients had a lower FEV1 (77.2% +/- 22.4 vs 86.7% +/-19.4, p=0.01) and a higher prevalence of P. aeruginosa (38.6 vs 17.5%, p<0.05). So in this population of CF children, a delay of 6.1 yr (vs 0.1 y) between diagnosis and referral to a specialist clinic resulted in poorer respiratory outcome at age 13 years. Most experienced CF clinicians are convinced that CF centre care is the ideal but all are not convinced.


A randomized, double-blind, placebo-controlled, international study (AIR-CF1 trial; June 2005 to April 2007), patients (n = 164; <or= 6 years of age) with FEV1 >or= 25% and <or= 75% predicted values, and no recent use of anti-Pseudomonal antibiotics or azithromycin were treated with 75 mg of AZLI (three times daily for 28 days) or placebo (1:1 randomization), then were monitored for 14 days after study drug completion. The primary efficacy end point was change in patient-reported respiratory symptoms. Secondary end points included changes in pulmonary function (FEV1), sputum PA density, and non-respiratory CFQ-R scales. After 28 days of treatment, AZLI improved the mean CFQ-R respiratory score (9.7 points; p < 0.001), FEV1 (10 3% predicted; p < 0.005), and sputum PA density (40% of AZLI vs 9% of placebo; p < 0.001), compared with placebo. The incidence of “productive cough” was reduced by half in AZLI-treated patients. PA aztreonam susceptibility at baseline and end of therapy were similar. So in patients with CF, PA airway infection, moderate-to-severe lung disease, and no recent use of anti-Pseudomonal antibiotics or azithromycin, 28-day treatment with AZLI significantly improved respiratory symptoms and pulmonary function, and was well tolerated. Also McCoy KS et al. Am J Respir Crit Care Med 2008; 178:921-928. [PubMed]


This group chaired by Dr Alan Smyth produced a very detailed and liberally referenced up to date account of the current recommendations for antibiotic use in people with CF in the UK. The recommendations differ significantly from those in N. America largely in the policy of early eradication of P. aeruginosa and the recommendation to use long term prophylactic anti-staphylococcal therapy for the first three years of life.

Dr Alan Smyth (figure 57) is Reader in Paediatrics at Nottingham University and Director of the Nottingham Paediatric CF Centre at the Nottingham City Hospital, UK.

The EarLy Inhaled Tobramycin for Eradication (ELITE) study was designed to assess the efficacy and safety of two regimens (28 and 56 days) of tobramycin inhalation solution (TIS) 300 mg/5 mL (TOBI(R)) twice daily for the treatment of early onset *P. aeruginosa* infection in CF patients. Children aged 6 months and over with early *P. aeruginosa* infection were treated for 28 days with TIS twice daily after which they were randomised to either stop or to receive a further 28 days treatment. The primary endpoint was the median time to recurrence of *P. aeruginosa* (any strain). Secondary endpoints included the proportion of patients free of *P. aeruginosa* infection one month after cessation of therapy and safety assessments.

The median time to recurrence of *P. aeruginosa* (any strain) was similar between the two groups. In total, 93% and 92% of the patients were free of *P. aeruginosa* infection one month after the end of treatment and 66% and 69% remained free after 27 months in the 28-day and 56-day groups, respectively. So treatment with inhaled tobramycin 28 days was an effective and well tolerated therapy for early *P. aeruginosa* infection in CF patients.


CF infants may be at increased risk of sodium depletion which may lead to impaired growth. The objective of this study was to evaluate their sodium supplementation requirements. Ten CF infants had serial measurements of weight and plasma/urine sodium and creatinine. Sodium supplementation was adjusted with the aim of maintaining fractional excretion (FENa) between 0.5% and 1.5% and urinary sodium > 10 mmol/L. The urine sodium:creatinine (UNa:Cr) ratio strongly correlated with FENa [UNa:Cr (mmol/mmol) = 35.0 x FENa (r=0.99)]. The FENa target range corresponded to UNa:Cr 17-52 mmol/mmol. All infants required sodium supplementation to achieve UNa:Cr > 17 mmol/mmol. Sodium supplement requirements (mean±/−SD) at ages 0-3, 3-6, 6-9 and 9-12 months were 1.9±/−0.5, 1.8±/−0.8, 1.9±/−0.9 and 0.8±/−0.4 mmol/kg/d. No infant required calorie supplementation to achieve expected weight gain. The authors concluded that using current UK CF Trust and European CFS guidelines many cases of sodium depletion may be overlooked. Some infants require more than the recommended 1-2 mmol/kg/d. The UNa:Cr ratio is a useful non-invasive measure to monitor sodium supplementation.

This is a particularly useful paper as most infants are diagnosed after neonatal screening and the advice in the UK and European CF Society consensus documents suggested that routine sodium supplementation was unnecessary.


CF carrier screening was offered to 3020 women and couples planning a pregnancy, or in early pregnancy, through obstetricians and general practitioners in Victoria, Australia from January 2006 to December 2008. Of the nine carrier couples, six were pregnant at the time of screening (five natural conception and one in vitro fertilisation) and all had CVS (mean gestation 12.5 weeks). Two fetuses were affected, three were carriers and one was not a carrier. Termination of pregnancy was undertaken for the affected fetuses. The authors concluded that carrier screening for CF by obstetricians and general practitioners by cheek swab sample can be successfully undertaken prior to pregnancy or in the early stages of pregnancy. Carrier screening was pioneered by David Brock in Edinburgh but abandoned there apparently as a result of the introduction of neonatal screening becoming available; also the improving prognosis was a factor. However, antenatal screening was recommended by a UK Health Technology Assessment report and even by the UK National Screening Committee but has not been implemented on the grounds of expense. Indeed it certainly seems to be an approach which should be available to future parents should they wish it.

A downward trend in the incidence of CF has been noted in northeastern Italy where antenatal screening is available (Castellani et al) [PubMed] and also in Edinburgh.


The authors searched Embase from 1987 through March 2008 for studies reporting the effect of treatment in a specialized or high-volume center or by subspecialists on clinically relevant outcomes. The authors concluded the available literature suggests that among patients with rheumatoid arthritis, diabetes mellitus or cystic fibrosis, outcomes are not superior in specialized centers or with subspecialists compared with other forms of chronic illness care.

This type of the Cochrane Review really exemplifies the limits of Cochrane Reviews!! It is of some concern where a conclusion is based merely on the published work that reviewers, who may be of relatively limited clinical experience, come to a conclusion which is different to that of generations of experienced CF physicians and families. It would be more helpful if reviewers were
to assess all the evidence, not merely only the trials which come up to their rigorous academic standards. Although it is unlikely that studies of this type will affect experienced clinicians’ firm conviction that centre care is preferable to local hospital care for people with CF, it is of some concern that such a study may be used by health care providers to deny patients funding to attend a specialist CF centre as has occurred in the past.


An increasing number of laboratories offering molecular genetic analysis of the CFTR gene and the growing use of commercial kits strengthen the need for an update of previous best practice guidelines (published in 2000). The importance of organizing regional or national laboratory networks, to provide both primary and comprehensive CFTR mutation screening, is stressed. Current guidelines focus on strategies for dealing with increasingly complex situations of CFTR testing. Diagnostic flow charts now include testing in CFTR-related disorders and in fetal bowel anomalies. Emphasis is also placed on the need to consider ethnic or geographic origins of patients and individuals, on basic principles of risk calculation and on the importance of providing accurate laboratory reports. Finally, classification of CFTR mutations is reviewed, with regard to their relevance to pathogenicity and to genetic counselling.


A retrospective study to evaluate the effectiveness of oxandrolone in improving the nutritional status and linear growth of pediatric patients with cystic fibrosis (CF). Both height z score (pre-Ox = -1.64 +/- 0.63, Ox = -1.30 +/- 0.49, P = .057) and weight velocity (pre-Ox = 4.2 +/- 3.7 kg/yr, Ox = 6.8 +/- 1.0 kg/yr, P = .072) showed beneficial trends that did not reach statistical significance. No adverse events were reported. The authors concluded oxandrolone improved the HV and BMI z score in patients with CF but larger studies were needed to determine if oxandrolone is an effective, safe, and affordable option to stimulate appetite, improve weight gain, and promote linear growth in patients with CF.

There were a number of papers on the use of anabolic steroids before more effective pancreatic enzymes became available (see Topic section anabolic steroids). Although the were effective, the side effects were a problem. Apparently there are fewer androgenic side effects with the newer preparation described in this paper.


Measurements of size, surface, acid resistance, release of enzymes, pharmacokinetics and batch consistency were undertaken. Available pancreatin preparations vary widely with respect to investigated parameters, which may have consequences for facilitating optimal management. This has always been the case.


P. aeruginosa was isolated in cough aerosols of 25 subjects (89%), 22 of whom produced sputum samples. P. aeruginosa from sputum and paired cough aerosols were indistinguishable by molecular typing. In four cases the same genotype was isolated from ambient room air. Approximately 70% of viable aerosols collected during voluntary coughing were of particles <=3.3 microm aerodynamic diameter. P. aeruginosa, Stenotrophomonas maltophilia and Achromobacter xylosidans were cultivated from respiratory particles in this size range. Positive room air samples were associated with high total counts in cough aerosols (p = 0.003). The magnitude of cough aerosols was associated with higher forced expiratory volume in 1 s (r = 0.45, p = 0.02) and higher quantitative sputum culture results (r = 0.58, p = 0.008).

One of a number of recent studies showing that during coughing, patients with CF produce viable aerosols of P aeruginosa and other Gram-negative bacteria of respirable size range, suggesting the potential for airborne transmission.

2009 Fuchs SI. Eder J. Ellemunter H. Gappa M. Lung clearance index: normal values,
The aim of this prospective study was to assess within-test repeatability, short term reproducibility and long term reproducibility, and to establish normal values for the LCI in healthy children and adolescents using the sidestream ultrasonic flow sensor (EasyOne Pro, MBW Module, ndd Medical Technologies, Switzerland). This study confirms the reliability and robustness of equipment, protocol and analysis and the reliability of the MBW technique in general. The present data will help to interpret the effect of therapeutic interventions and interpretation of longitudinal data in patients with pulmonary diseases.

Further evidence that this test does seem to be an extremely useful. It is also applicable to young children with CF.

In the last few years there has been a growing interest in lung clearance index (LCI), a measure of lung physiology derived from multiple breath washout tests. This resurgence of interest was initially driven by the recognition that such assessments were capable of detecting early airways disease in children, and are more sensitive and easier to perform in this population than conventional lung function tests [Aurora P, Kozlowska W, Stocks J. Gas mixing efficiency from birth to adulthood measured by multiple-breath washout. Respir Physiol Neurobiol, 2005;148(1-2):125-39]. With an appreciation of the importance of earlier identification of airways dysfunction, and prevention of irreversible structural airway changes, methods of following airways disease in these “silent years” are especially important. LCI has now been reported in studies involving all age groups, from infants to adults [Lum S, Gustafsson P, Lungberg H, Hulskamp G, Bush A, Carr SB, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax, 2007;62(4):341-7; Horsley AR, Gustafsson PM, Macleod K, Saunders CJ, Greening AP, Porteous D, et al. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax, 2008;63:135-40], and has a narrow range of normal over this wide age range, making it especially suitable for long-term follow-up studies. In cystic fibrosis (CF) particularly, there is a pressing need for sensitive and repeatable clinical endpoints for therapeutic interventions [Rosenfeld M. An overview of endpoints for cystic fibrosis clinical trials: one size does not fit all. Proc Am Thorac Soc, 2007;4(4):299-301], and LCI has been proposed as an outcome measure in future CF gene therapy studies [Davies JC, Cunningham S, Alton EW, Innes JA. Lung clearance index in CF: a sensitive marker of lung disease severity. Thorax, 2008;63(2):96-7]. This review will consider how LCI is derived, how it differs from conventional lung function testing, and its applications and limitations.

This is an excellent review of lung clearance index with many useful references so the abstract has been included in full. Does seem to be an important, applicable advance in respiratory function testing particularly for children

Increased large artery stiffness occurs in a range of inflammatory conditions indicating an ageing of the vasculature and additionally being an independent risk factor for cardiovascular events. Augmentation index (AIx) is increased in adults with CF, in the presence of a normal blood pressure and independent of diabetic status. AIx was related to the systemic inflammatory status. These findings have implications for management and require further exploration so that cardiovascular health can be maintained.

As more adults are studied new findings arise. This contrasts with a previous report that there was a reduction in atheroma in patients with CF.

Small intestine bacterial overgrowth is frequent in cystic fibrosis: combined hydrogen and methane measurements are required for its detection.

The study aimed to assess the usefulness of combined measurement of hydrogen and methane expiration for the diagnosis of SIBO in CF. The study comprised 62 CF patients aged 5 to 18 years. Three-hundred-ninety subjects assessed due to gastrointestinal symptoms for the presence of SIBO served as a comparative group. In all subjects hydrogen/methane BT using glucose was performed. In 23 (37.1%) CF patients and in 52 (13.3%) subjects from the comparative group abnormal BT results were found. In seven (11.3%) CF patients and 29 (7.4%) of the other subjects studied methane measurement allowed diagnosis of SIBO. The authors confirmed that small intestine bacterial overgrowth is frequent in cystic fibrosis. They advised that for its detection in cystic fibrosis and other gastrointestinal patients, combined hydrogen and methane measurement instead of hydrogen breath test should be applied. Without the additional measurement of methane a significant percentage of SIBO will be missed.

There are a number of studies now showing that SIBO is relatively common in people with CF although in most CF centres where attention is largely directed towards the chest the knowledge does seem to excite much interest! The finding can also be considered in the light of reports that the use of probiotics may reduce the frequency of exacerbations of chest infection.

2009 Simmonds NJ. Cullinan P. Hodson ME. Growing old with cystic fibrosis - the

The proportion of patients with cystic fibrosis (CF) who are middle-aged is increasing - and is likely to continue to do so. We surveyed a population of long-term CF survivors to assess their burden of illness and profile their disease characteristics. The full spectrum of disease is represented in this population and, importantly, 30% are DeltaF508 homozygous. Provision needs to be made for the healthcare needs of this increasing population of older patients.

This is invaluable experience from the largest adult CF centre in the world.


A multicenter prevalence study of nontuberculous mycobacteria (NTM) involving 1,582 patients (mean age, 18.9 years; male/female ratio, 1.06) with cystic fibrosis in France. The overall NTM prevalence (percentage of patients with at least one positive culture) was 6.6% (104/1,582 patients), with prevalences ranging from 3.7% (in the east of France) to 9.6% (in the greater Paris area). Mycobacterium abscessus complex (MABSC; 50 patients) and Mycobacterium avium complex (MAC; 23 patients) species The "new" species, Mycobacterium bolletii and Mycobacterium massiliense, accounted for 40% of MABSC isolates. MABSC species were isolated at all ages, with a prevalence peak between 11 and 15 years of age (5.8%), while MAC species reached their highest prevalence value among patients over 25 years of age (2.2%).


A retrospective analysis of sputum microbiology from adult CF patients (1985 to 2005) using the Royal Brompton Hospital CF database. Infection with Pseudomonas aeruginosa or Staphylococcus aureus between 1985 and 2005 remained stable (77 to 82%, p=0.159; 54 to 47%, p=0.108; respectively). Haemophilus influenzae (48 to 6%; p<0.001), Aspergillus species (18 to 9%; p=0.002) and Burkholderia cepacia complex (9 to 4%; p=0.041) prevalence decreased. Stenotrophomonas maltophilia and MRSA increased (1 to 4%, p=0.02; 1 to 6%, p=0.002, respectively). So P. aeruginosa infection remained stable; there has been a decline in B. cepacia complex, H. influenzae and Aspergillus sp., and only a small increase in S. maltophilia and MRSA. Intensive antibiotic strategies have been employed, which, so far, have not resulted in clinically significant emergence of new pathogens.

This is a useful record of the microbiological situation at the Royal Brompton Hospital in London. Interesting that the prevalence of Aspergillus has fallen as some centres have seen a rise in this fungus over recent years.


Data from the Cystic Fibrosis Foundation Patient Registry were used to examine trends in the incidence and prevalence of bacterial pathogens isolated from patients with CF in the United States from 1995 to 2005. The number of patients with CF in the patient registry increased from 19,735 in 1995 to 23,347 in 2005. During the study period, the annual prevalence of Pseudomonas aeruginosa significantly declined from 60.4% in 1995 to 56.1% in 2005 (p < 0.001). The decline was most marked in children 6 to 10 years old (48.2 to 36.1%) and adolescents 11 to 17 years old (68.9 to 55.5%). Both the incidence (21.7% in 1995 and 33.2% in 2005) and prevalence (37.0% in 1995 and 52.4% in 2005) of methicillin-susceptible Staphylococcus aureus significantly increased and the age-specific prevalence was highest in patients 6 to 17 years old. The prevalence of methicillin-resistant S aureus increased from 0.1% in 1995 to 17.2% in 2005 and from 2002 to 2005 was highest in adolescents 11 to 17 years old. Both the prevalence and incidence of Burkholderia cepacia complex declined, while the prevalence of Haemophilus influenzae, Stenotrophomonas maltophilia, and Alcaligenes xylosoxidans increased. Data from the patient registry suggest that the epidemiology of bacterial pathogens in patients with CF changed during the study period.

The prevalence of both S.aureus and P. aeruginosa are higher in the USA than in UK and particularly in UK centres where both anti-staphylococcal prophylaxis and early eradication of Pseudomonas are routine.


The authors identified people with CF in the USA who were currently receiving medical care for the disorder and characterized their medical expenditures during the period 2004-2006. The annual medical care expenditure for a person with actively managed CF averaged $48,098 in 2006 dollars, which was 22 times higher than for a person without CF. This ratio is high relative to other chronic disorders. Outpatient prescription medications made up the largest component of total expenditures for people with CF (39%). Those who were recorded in claims data as having a liver or lung transplant, malnutrition, diabetes, or a chronic Pseudomonas aeruginosa pulmonary infection incurred much higher expenditures than people without these conditions. People with CF
will incur high medical expenditures throughout their life span. These findings will assist in the development of economic evaluations of future CF screening and management initiatives.

This study confirms the very high cost of CF care which is likely to be similar in the UK. Both the absolute cost and the unfavourable comparison with other chronic disorders presents a major problem which is likely to increase as a greater proportion of the CF population are adults.


A report of two patients with asthma whose NP dramatically reduced in size after a course of MTX therapy administered as an additional treatment for their steroid-dependent asthma.

Although these patients had asthma it is interesting that they responded to methotrexate - it is possible that the minority of people with severe recurring nasal polyps may also respond.


Sleep impairment has been described in patients with cystic fibrosis (CF). Pain is a known cause of sleep disturbance and as pain is commonly reported in patients with CF, we sought to find an association between impaired sleep quality and pain. Fifty adult CF patients completed surveys of pain and sleep quality. We found that pain and poor sleep quality are reported in a majority of adult CF patients and there is a strong correlation between the two. This will have important clinical implications in the evaluation and treatment of adult patients.

There are more reports and attention paid to chronic pain which is very common in people with CF. In this study from the USA the pain was contributing significantly to sleep disturbance in many patients.


In this European consensus document we review the current status of inhaled medication in CF, including the mechanisms of action of the various drugs, their modes of administration and indications, their effects on lung function, exacerbation rates, survival and quality of life, as well as side effects.

A detailed consensus document with no less than 249 references.


A useful review article on the optimal perioperative management of patients with CF requires an understanding of the relevant pathophysiology and the unique challenges presented by these patients. The authors reviewed these concepts, including special considerations such as liver and lung transplantation and pregnancy.

These are particularly important as not infrequently a person with CF is admitted to a surgical unit where there is limited knowledge of CF - for example postoperatively enzymes may be omitted leading to DIOS and serious unnecessary complications.


The biggest article so far on wrinkling confirms the association between aquagenic wrinkling of the palms and CF. Among patients with CF, greater AWP occurs in those who are homozygous for the DeltaF508 mutation.


The Cystic Fibrosis Foundation established a committee to define the key questions related to pulmonary exacerbations, review the clinical evidence using an evidence-based methodology, and provide recommendations to clinicians.


To determine the clinical relevance of Mycobacterium chelonae-abscessus group isolation from clinical samples we retrospectively reviewed medical files of all patients from whom these mycobacteria were isolated between January 1999 and January 2005. We applied the American Thoracic Society (ATS) diagnostic criteria to establish clinical relevance. Ninety-five patients were traced (56 M. chelonae, 25 Mycobacterium abscessus, 8 Mycobacterium massiliense, 6 Mycobacterium bolletii). Most isolates were cultured from pulmonary samples in patients with pre-existing pulmonary disease. Among patients with pulmonary isolates, 27% (20/74) meets ATS criteria; M. abscessus is most relevant (50%; 9/18), followed by M. massiliense (29%; 2/7), M. bolletii (20%; 1/5) and M. chelonae (18%; 8/44). Extrapulmonary disease presented as disseminated skin disease, eye disease specific for M. chelonae and otomastoiditis for M.
abscessus. Treatment, especially for pulmonary M. abscessus disease, yielded limited results. One-fourth of the patients with pulmonary M. chelonae-abscessus group isolates met the ATS criteria; this percentage differs by species. Species distribution and clinical relevance differ from other regions. M. abscessus isolation in cystic fibrosis patients warrants special attention. Current ATS criteria might be too lenient to diagnose M. chelonae-abscessus group disease.

Increasing interest in NTM in CF. This survey gives an idea of the general prevalence of the various NTMs.


Patients with chronic Pseudomonas aeruginosa colonization received two successive courses of intravenous tobramycin and ceftazidime (200 mg/kg of body weight/day) for pulmonary exacerbation administered as thrice-daily short infusions or as a continuous infusion. The continuous infusion of ceftazidime appeared to be as efficient as short infusions in patients with cystic fibrosis as a whole, but it gave better results in patients harboring resistant isolates of P. aeruginosa.

Ideally a steady blood level of ceftazidime should be maintained during treatment in contrast to aminoglycosides where peak levels are ideal. Previous studies have shown continuous infusion of CZ to be more satisfactory and are recommend for maximum effect - for example when attempting to eradicate Pseudomonas. It is interesting that better result were obtained in the present study when treating resistant bacteria.


The pharmacokinetics and pharmacodynamics of a novel liposomal amikacin for inhalation were evaluated in cystic fibrosis patients with chronic pseudomonas infection. Twenty-four patients from two studies received 500 mg of liposomal amikacin by inhalation once daily for 14 days. While significant relationships between absolute change in PFT endpoints and the ratio of serum or sputum area under the concentration-time curve to the MIC (AUC/MIC) were not observed, relationships between change in log10 CFU and serum AUC/MIC ratio and change in log10 CFU and absolute changes in all PFT endpoints were significant. Together, these findings likely represent drug effect and warrant the further development of liposomal amikacin for inhalation.

One of the few new antibiotic preparations which are going forward for further evaluation.


Cystic fibrosis (CF)-related diabetes (CFRD) diagnosis and management have considerably changed since diabetes was first shown to be associated with a poor prognosis in subjects with CF. Current trends in CFRD prevalence, incidence, and mortality were determined from a comprehensive clinical database. Data were reviewed from 872 CF patients followed at the University of Minnesota during three consecutive intervals: 1992-1997, 1998-2002, and 2003-2008. CFRD is currently present in 2% of children, 19% of adolescents, and 40-50% of adults. Incidence and prevalence are higher in female subjects aged 30-39 years; otherwise, there are no sex differences. In younger individuals, CFRD without fasting hyperglycemia predominates, but fasting hyperglycemia prevalence rises with age. CFRD mortality has significantly decreased over time. From 1992-1997 to 2003-2008, mortality rate in female subjects dropped by >50% from 6.9 to 3.2 deaths per 100 patient-years and in male subjects from 6.5 to 3.8 deaths per 100 patient-years. There is no longer a sex difference in mortality. Diabetes was previously diagnosed as a perimorbid event in nearly 20% of patients, but of 61 patients diagnosed with diabetes during 2003-2008, only 2 died. Lung function but not nutritional status is still worse in CF patients with diabetes compared with those without diabetes. Nutritional status and pulmonary status are similar between patients without fasting hyperglycemia and those with fasting hyperglycemia.

CONCLUSIONS: Previously noted sex differences in mortality have disappeared, and the gap in mortality between CF patients with and without diabetes has considerably narrowed. We believe that early diagnosis and aggressive treatment have played a major role in improving survival in these patients.

A useful review of changes in the features of CFRD by Antoinette Moran an expert on CFRD from Minnesota.


To determine the prevalence and severity of tracheomalacia in adults with cystic fibrosis (CF) by using dynamic cine multidetector computed tomography (MDCT). To correlate these findings with pulmonary function test (PFT) results and the severity of parenchymal lung disease. Tracheomalacia was demonstrated in 24 (69%) patients and no control subjects during forced expiratory maneuvers (P = .001) and in 10 (29%) patients and one (10%) control subject during coughing. There was no correlation between tracheal cross-sectional luminal reduction and either predicted FEV(1) or CT Bhalla score. Tracheomalacia depicted at dynamic cine multidetector CT is
a highly prevalent finding in adults with CF.

Clinically tracheomalacia has been observed on occasion but the present study demonstrates how common is the condition. It is interesting that similar tracheal abnormalities occur commonly in CF pigs in particular some degree of maldevelopment of the tracheal cartilage.

A single-centre, randomised, double-blinded, placebo-controlled phase II clinical study to test safety and efficacy of a 12-week therapy with low-dose (700 mg/daily) or high-dose (2800 mg/daily) of NAC. High-dose NAC was a well-tolerated and safe medication but did not alter clinical or inflammatory parameters. However, extracellular glutathione in induced sputum tended to increase on high-dose NAC. The authors concluded that high-dose NAC is a well-tolerated and safe medication for a prolonged therapy of patients with CF with a potential to increase extracellular glutathione in CF airways.

This study confirms the generally perceived lack of clinical effect of N-acetylcysteine on the respiratory function and inflammatory parameters but the increase in extracellular glutathione may be of some benefit. It is difficult to reconcile the lack of clinical effect with some of the early reports showing marked increase in the volume of sputum; also the clinical experience suggesting some benefit. The effects are complicated - even recently it has been reported that that NAC causes a significant efflux of Cl from CF bronchial epithelial cells (Veralogian I et al). [PubMed]

Increasing the magnesium concentration in the airway surface liquid by aerosolisation of magnesium solutions or oral magnesium supplements could improve the removal of highly viscous mucus in chronic lung disease by activating endogenous DNase activity.

An interesting observation as magnesium had already been involved in failure of DNase therapy in people with CF (Sanders NN et al. 2006. [PubMed].

Theoretical concerns about liver disease and vitamin A deficiency have limited the use of oral isotretinoin for troublesome acne in adolescents with cystic fibrosis. Oral isotretinoin was administered to nine patients with cystic fibrosis who had troublesome acne unresponsive to antibiotics. All patients were followed for 1-4 years after cessation of treatment. Isotretinoin treatment cleared active acne lesions in all patients. It was well-tolerated, and no patient had significant side effects. All nine patients were pleased or delighted with the improvement in their skin. Adolescents with cystic fibrosis and acne can be treated with oral isotretinoin. Oral isotretinoin should be considered for adolescents with cystic fibrosis who have acne associated with scarring, acne not clearing with topical and antibiotic treatment, acne associated with depression or severe cystic acne.

This is a helpful paper for those considering the use of isotretinoin but who may have reservations regarding liver toxicity.

There was also a strong relationship between leucine rate of appearance (a measure of protein catabolism) and IGF-I. These results suggest a strong correlation between IGF-I and height, weight and protein catabolism and emphasize the need to normalize IGF-I levels in children with cystic fibrosis.

Hardin has written a number of papers on the use of growth hormone. Here the authors analyze the IGF-1 levels in the patients with CF previously studied. It is interesting that in recent animal studies involving CF pigs there seems to be a relationship between IGF-1 and the growth potential of the affected animals (Rogan MP et al. 2010). [PubMed]

Amitriptyline, a blocker of acid sphingomyelinase and acid ceramidase, significantly reduces Pseudomonas aeruginosa lung infection in cystic fibrosis (CF) mice with concurrent increase of survival [PubMed]. Our aim was to establish whether amitriptyline is safe and effective in the treatment of CF patients. In a randomised, double-blinded, placebo-controlled, cross-over pilot study, 4 adult CF patients received 37.5 mg of amitriptyline or placebo twice daily for 14 days. Subsequently in a phase II study 19 adult CF patients were randomly allocated to three treatment groups receiving amitriptyline once daily for 28 days at doses of 25 mg (n=7), 50 mg (n=8), or 75 mg (n=8) or placebo (n=13). The primary outcome was the difference of forced expiratory volume in 1 sec (FEV(1)) at day 14 between amitriptyline and placebo. Primary endpoint measures improved significantly in three of the four patients in the pilot study after amitriptyline treatment vs placebo (relative FEV(1): 14.7+/−5%; p = 0.006) and in the 25 mg treatment group of the phase...
In recent years, S. maltophilia is more frequently isolated from people with CF and although it is more frequently isolated in animals with chronic respiratory disease. Schweizer Archiv fur Tierheilkunde 2009; 151:323-328. [PubMed]

Stenotrophomonas maltophilia (S. maltophilia) is frequently isolated from humans with cystic fibrosis. Seven strains of S. maltophilia isolated from animals are described, of which 5 strains were harvested from 3 horses, a dog and a cat with chronic respiratory disease. Analysis with pulsed field gel electrophoresis revealed that 2 horses, which were boarded in the same clinic but two years apart, harboured the same strain of S. maltophilia.

In recent years, S. maltophilia is more frequently isolated from people with CF and although the organism appears to be ubiquitous, it is useful to know that animals are one potential source.

Young children with CF (111) who have upper and lower airway P. aeruginosa infection determined by BAL have increased endobronchial inflammation and poorer clinical status compared with those with only upper airway P. aeruginosa infection. The independent and additive effects of S. aureus on inflammation support the significance of polymicrobial infection in early CF lung disease.

These findings could have been predicted and are not unexpected. The additive effect of S. aureus is important and should increase the efforts to avoid chronic S. aureus infection in addition to P. aeruginosa.

Screening newborns for cystic fibrosis (CF) is considered to be an ethical undertaking in regions with a significant incidence of the condition. Current screening protocols result in recognition of infants with an equivocal diagnosis. A survey of European practice suggested inconsistencies in the evaluation and management of these infants. We have undertaken a consensus process using a modified Delphi method. This has enabled input of CF specialists from a wide geographical area to a rigorous process that has provided a clear pathway to a consensus statement. A core group produced 21 statements, which were modified over a series of three rounds (including a meeting arranged at the European CF Conference). A final document of 19 statements was produced, all of which achieved a satisfactory level of consensus. The statements cover four themes; sweat testing, further assessments and investigations, review arrangements and database. This consensus document will provide guidance to CF specialists with established.

As neonatal screening has now been widely adopted it is likely that not all infants who are
detected as possibly having CF will be seen at CF centres. Therefore this document provides good evidence based on experience of the contributors for dealing with the infant where the diagnosis is in doubt. There is a helpful list of most of the eventualities that one is likely to encounter. In my experience of over 20 years of neonatal CF screening in Leeds these cases are the exception.


This consensus document states the focus of management is on maintaining health by preventing nutritional and respiratory complications. The CF Foundation convened a committee to develop recommendations based on a systematic review of the evidence and expert opinion. These guidelines encompass monitoring and treatment recommendations for infants diagnosed with CF and are intended to help guide families, primary care providers, and specialty care centers in the care of infants with CF.


Cystic fibrosis-related diabetes (CFRD) without fasting hyperglycemia (CFRD FH-) is not associated with microvascular or macrovascular complications, leading to controversy about the need for treatment. The Cystic Fibrosis Related Diabetes Therapy (CFRDT) Trial sought to determine whether diabetes therapy improves BMI in these patients. A three-arm multicenter randomized trial compared 1 year of therapy with premeal insulin as part, repaglinide, or oral placebo in subjects with cystic fibrosis who had abnormal glucose tolerance. One hundred adult patients were enrolled. Eighty-one completed the study, including 61 with CFRD FH- and 20 with severely impaired glucose tolerance (IGT). During the year before therapy, BMI declined in all groups. Among the group with CFRD FH-, insulin-treated patients lost 0.30 +/- 0.21 BMI units the year before therapy. After 1 year of insulin therapy, this pattern reversed, and they gained 0.39 +/- 21 BMI units (P = 0.02). No significant change in the rate of BMI decline was seen in placebo-treated patients (P = 0.45). Repaglinide-treated patients had an initial significant BMI gain (0.53 +/- 0.19 BMI units, P = 0.01), but this effect was not sustained. After 6 months of therapy they lost weight so that by 12 months there was no difference in the rate of BMI change during the study year compared with the year before (P = 0.33). Among patients with IGT, neither insulin nor repaglinide affected the rate of BMI decline. Significant differences were seen in the rate of lung function decline or the number of hospitalizations in any group. CONCLUSIONS: Insulin therapy safely reversed chronic weight loss in patients with CFRD FH-.

A conclusive result showing that insulin improves the nutritional state of people with CF who have impaired glucose tolerance without fasting hyperglycemia


Continuity of care has been explored largely from academic and service provider perspectives, and in relation to adult patient/client groups. We interviewed parents of children with complex chronic health conditions to examine how their experiences and perceptions of continuity of care fit with these perspectives; and to identify the salient factors in the experience of, and factors contributing to, continuity in this population. A thorough knowledge of the child on the part of service providers emerged as extremely important to parents; such knowledge was underpinned by continuity of personal relationships, principally, and also by written information. For this population, notions of continuity extend to the full range of service providers these children and families need to achieve optimal health status, and are not limited to physicians and nurses. Communication among providers was seen as integral to perceived continuity. Compartmentalization of services and information led to parents assuming a necessary, though at times, uncomfortable, coordinating role. Geographic factors, institutional structures and practices, provider attitudes, and, on occasion, parent preferences and judgments, were all found to create barriers to "seamless" management and provision of care continuity across providers, settings, and sectors.

Although the authors suggest that "These findings add new perspectives to the understanding of continuity within chronically ill children's health care. They are relevant to contemporary initiatives to improve continuity of services to children with special health care needs, demonstrate the need for parental support of their important role in maintaining continuity, and suggest avenues for further research", they are of course the basic principles upon which good care for CF is organised in the best CF centres.


A multicenter prevalence study of nontuberculous mycobacteria (NTM) involving 1,582 patients (mean age, 18.9 years; male/female ratio, 1.06) with cystic fibrosis in France. The overall NTM prevalence (percentage of patients with at least one positive culture) was 6.6% (104/1,582 patients), with prevalences ranging from 3.7% (in the east of France) to 9.6% (in the greater Paris area). Mycobacterium abscessus complex (MABSC; 50 patients) and Mycobacterium avium
A useful large survey of NTM in France showing an overall prevalence of 6.6%.


Phenotypic variability associated with certain mutations makes genetic counselling difficult, notably for R117H, whose disease phenotype varies from asymptomatic to classical CF. The high frequency of R117H observed in CF newborn screening has also introduced diagnostic dilemmas. The aim of this study was to evaluate the disease penetrance for R117H in order to improve clinical practice. The phenotypes in all individuals identified in France as compound heterozygous for R117H and F508del, the most frequent CF mutation, were described. The allelic frequencies of R117H (p(R117H)), on either intron 8 T5 or T7 background, and F508del (p(F508del)) were determined in the French population, to permit an evaluation of the penetrance of CF for the [R117H]+[F508del] genotype. Clinical details were documented for 184 [R117H]+[F508del] individuals, including 72 newborns. The disease phenotype was predominantly mild; one child had classical CF, and three adults severe pulmonary symptoms. In 5245 healthy adults, p(F508del) was 1.06%; p(R117H;T7) 0.27% and p(R117H;T5)<0.01%. The theoretical number of [R117H;T7]+[F508del] individuals in the French population was estimated at 3650, whereas only 112 were known with CF related symptoms (3.1%). The penetrance of classical CF for [R117H;T7]+[F508del] was estimated at 0.03% and that of severe CF in adulthood at 0.06%. The authors suggest that these results suggest that R117H should be withdrawn from CF mutation panels used for screening programmes. The real impact of so-called disease mutations should be assessed before including them in newborn or preconceptional carrier screening programmes.


The Early Pseudomonas Infection Control (EPIC) program consists of two studies, a randomized multicenter trial in CF patients ages 1-12 years at first isolation of Pa from a respiratory culture, and a longitudinal cohort study enrolling Pa-negative patients. Using a factorial design, trial participants are assigned for 18 months to either anti-pseudomonal treatment on a scheduled quarterly basis (cycled therapy) or based on recovery of Pa from quarterly respiratory cultures (culture-based therapy). The study drugs include inhaled tobramycin (300 mg BID) for 28 days, combined with either oral ciprofloxacin (15-20 mg/kg BID) or oral placebo for 14 days. The primary endpoints of the trial are the time to pulmonary exacerbation requiring IV antibiotics or hospitalization for respiratory symptoms, and the proportion of patients with new Pa-positive respiratory cultures during the study.

This major N. American study into the early eradication of Pseudomonas is welcome. The dose of tobramycin would seem to be unnecessarily large as judged by experience from successful European trials some years ago.


To review the outcomes of offering carrier testing for cystic fibrosis (CF) to couples considering pregnancy, and to women in early pregnancy and their partners. An after-hours clinic was established in Newcastle for discussion of issues related to prenatal testing. Couples were offered CF carrier testing by extracting DNA from a mouthwash sample. An expanded one-step model was used with both partners being tested initially for the p.F508del cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation. If one partner was a p.F508del carrier, the other partner was tested for an additional 28 CFTR mutations. Of 1000 individuals who were offered CF carrier testing, none declined. No re-collections of mouthwash samples were required, and results were available within 14 days. There were 730 individuals who had no family history of CF (73%); 27 were carriers (4%; 95% CI, 2.4%-5.3%), and there were two high-risk couples where both partners were carriers of p.F508del. There were 270 individuals who had an affected family member with CF or a child identified as a CF carrier through newborn screening; 126 were carriers (46%; 95% CI, 40.6%-52.8%), and there were two high-risk couples - one couple where both partners were carriers of p.F508del, and another couple where the woman was homozygous for p.F508del and the man was a p.F508del carrier. The information on carrier status led the four high-risk couples to change their reproductive decisions to avoid having a child with CF.

The authors concluded that CF carrier testing for couples using an expanded one-step model will detect about 80% of high-risk couples and enables various reproductive choices. They believe that couples considering pregnancy, and women in early pregnancy and their partners, should be offered CF carrier testing.