To determine the prevalence of Burkholderia cepacia from the environment in a regional adult cystic fibrosis (CF) care centre. B. cepacia was not detected from commonly shared items of equipment, staff hands, staff uniforms or toilets. In addition, the organism was not detected in toilet bowls, even in the B. cepacia unit. With regard to positive environments for B. cepacia, 4/10 (40%) of the outside surfaces and inner rims of patients’ plastic disposable sputum collection containers and 4/17 (23.5%) of air from patients’ rooms, following physiotherapy, were positive. All positive samples originated in the B. cepacia segregation area of the inpatient wards and B. cepacia was not detected in the non-cepacia area of the CF centre. Consequently, these two positive sites should therefore be treated as high risk, where organisms may be potentially transmitted from environment to patient.

A useful study confirming that B.cepacia only appeared to be a potential problem in areas inhabited by CF patients already infected by the organism.

This study demonstrates extensive spread of a single, clonal strain of *P. aeruginosa* in a large pediatric CF clinic. Whether such a strain is also more virulent than sporadic isolates remains to be determined however the fatal outcome for 5 of these children suggests this was almost certainly the case. As transmissible strains could emerge elsewhere, the authors suggested that other CF clinics may also need to consider molecular methods of surveillance for cross-infection. This is a really tragic story and further evidence of the potential and at times very real dangers of spread of highly transmissible strains of *P. aeruginosa*. The fact the 5 children died attests to this strains virulence and this type of highly transmissible infection also leads to a requirement for more treatment (Jones AM et al. 2002 below). This is another study recommending to others that molecular methods should be used when studying cross infection in CF centres. It is interesting and of some concern that around this time in some major CF centres, there were still clinicians who doubted the need for segregation even though the first major epidemic had been described in 1996 from Liverpool (Cheng et al, 1996 above)

This is a really tragic story and further evidence of the potential and at times very real dangers of spread of highly transmissible strains of *P. aeruginosa*. The fact the 5 children died attests to this strains virulence and this type of highly transmissible infection also leads to a requirement for more treatment (Jones AM et al. 2002 below). This is another study recommending to others that molecular methods should be used when studying cross infection in CF centres. It is interesting and of some concern that around this time in some major CF centres, there were still clinicians who doubted the need for segregation even though the first major epidemic had been described in 1996 from Liverpool (Cheng et al, 1996 above)

The results confirmed wide mutational heterogeneity throughout the world. They also examined CF incidence, DeltaF508 frequency, and regional mutational heterogeneity in a subset of populations and there is a significant positive correlation between DeltaF508 frequency and the CF incidence levels of regional populations. Regional analyses were also performed to search for trends in the distribution of CFTR mutations across migrant and related populations; this led to clarification of ancestry-genotype patterns that can be used to design CFTR multi-mutation panels for CF screening programs.

This is an immense study bringing together all the information from over 100 published papers to achieve a global understanding of the population molecular genetics associated with CF in an effort to increase understanding of ancestry-genotype relationships, to compare mutational arrays with incidence and to gain insight for decisions regarding screening program enhancement through CFTR mutational analysis.
2002 Journal of Cystic Fibrosis is launched. Dr Harry Heijerman is the founder editor. This new journal, the first devoted entirely to cystic fibrosis, was launched in January 2002 and is the official journal of the European Cystic Fibrosis Society. Dr Harry Heijerman was the Founding Editor and under his guidance the journal was increasingly successful; the editorship was taken over by Prof. Gerd Döring in 2006.

Fig. 27: Dr Harry Heijerman

Harry Heijerman (figure 27) is Physician at Haga Teaching Hospital, Deb Haag in the Netherlands. He is a leading figure in CF in Europe and Medical Advisor to CF Worldwide.

The CF Foundation's Therapeutics Development Network conducted 18 clinical trials in 3.5 years and the concept is a major advance in accelerating the introduction of new treatments which can be painstakingly slow. The Network uses internet applications for study conduct and communication, the development of statistical methodology to enhance the efficiency of clinical trial design, the development of outcome measures specific to CF and an infrastructure necessary for expediting protocol development. This was a very successful initiative of the CF Foundation to speed the progress of potentially useful treatments into clinical use for patients. The CF Foundation funded the network of centres and specialist nurses to speed the clinical trials and thus the introduction of new treatments.

The progress of 41 totally CF Centre-treated patients, 23 who came to the CF centre annually for review and 41 treated in close cooperation between the CF Centre and local hospitals. After 3 years there were no significant differences in pulmonary function, nutritional status or microbiological status. The authors conclude the results - could signify that local paediatricians have a special role in the care of patients with CF in close cooperation with the specialist centre”.

So should every patient attend a CF Centre as recommended by virtually all experienced CF clinicians since the Sixties? There is still considerable discussion on this question. This study is reassuring as it provides some support for the concept of shared-care“ which, like it or not, is still widely practised in the UK and elsewhere. There is an appropriate standard, condoned in the CF Trust’s Standards of Care document, but shared care is not recommended for adults. It is possible that as regimens of treatment become more established and standardised, the care at smaller local clinics will approach that at CF centres. However, there are still some children attending their local hospital with only sporadic visits to and advice from the staff at the Specialist CF Centre which is unsatisfactory. Also the numbers in this present study are small to the extent that the question is not finally answered. Obviously local conditions and facilities will determine the most appropriate arrangements.

Fig. 28: Professor Andy Bush

2002 Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. Lancet 2002; 360:978-84. A major UK trial of macrolides from the Royal Brompton Hospital, London following the report of Jaffe et al, 1998 (above). 41 children with CF received either azithromycin or placebo for 6 months in addition to their usual treatments. The median relative difference in FEV1 between azithromycin and placebo patients was 5.4%. However, this was made up as follows - FEV1 of 13 (31.7%) patients improved by more than 13% but five (12.2%) deteriorated by more than 13% (p=0.059). Seventeen (41.5%) of the azithromycin treated patients required fewer oral antibiotic courses but five had extra courses (p=0.005). Sputum bacterial densities, inflammatory markers, exercise tolerance, and subjective well-being did not change. There were no noticeable side-effects.

This was an important trial as it gave further support to one of the major new treatments of the Millennium which would become widely used not only in patients chronically infected with Pseudomonas but eventually also in younger uninfected patients. However, the clear importance of considering the effect of treatment on individual patients is apparent as the FEV1 of five children deteriorated by more than 13%. It is interesting, and perhaps not without relevance in regard to the effects of macrolides, that Harry Shwachman used erythromycin on more severely affected patients and at times saw significant benefit. Also Margaret Mearns in London used erythromycin in the young patients - perhaps they appreciated that there was some additional effect from the macrolides? By 2006 no less than 57.3% of patients with CF in the USA were taking regular azithromycin.

Prof. Andy Bush (figure 28) is paediatrician at the Royal Brompton Hospital, London and has been a leading researcher and clinician involved in CF from the early Nineties. This is one of the many
P. aeruginosa treatment with penicillin and aureomycin); subsequently when is eradicated and S. aureus pathogen from the environment colonizes and, if not treated, infects the airway. For example when it seems that if an organism is eradicated from the airways of a person with CF another potential and prevented other environmental organisms appear particularly Aspergillus fumigatus and Stenotrophomonas maltophilia (noted both in the Copenhagen and Leeds CF centres). But this is not a good reason to fail to eradicate any potential pathogens, symptoms or not, as they appear which is the policy in many European CF centres. Finally, it should be noted that it is not essential to give long term fluocoxacillin to achieve a very low prevalence of S. aureus infection. An alternative is to culture regularly (every clinic attendance and also when unwell) as is the policy in some European centres and treat vigorously whenever S. aureus appears (Szaff and Holby, 1981 above - see discussion after this entry for more on anti-Staphylococcal prophylaxis).

The plan of this study was reported some 10 years previously at the 1992 N American CF Conference by Dr Stutman but the results not published until 2002. This study with cephalxin,(a broader spectrum antibiotic than fluocoxacillin) does not provide useful information about the use of long term fluocoxacillin (currently recommended for the first 3 years for all CF infants by the UK CF Trust Antibiotic Working Group 2009). Also during the study early eradication treatment of P. aeruginosa was not practiced in the USA. In UK centres where both long term fluocoxacillin AND early P. aeruginosa eradication is routine the prevalence of both chronic S. aureus and P. aeruginosa is very low (Lee et al, 2004). [PubMed]

It seems that if an organism is eradicated from the airways of a person with CF another potential pathogen from the environment colonizes and, if not treated, infects the airway. For example when S. aureus is treated, P aeruginosa appears (a fact noted since the early days of CF antibiotic treatment with penicillin and aureomycin); subsequently when P. aeruginosa is eradicated and prevented other environmental organisms appear particularly Aspergillus fumigatus and Stenotrophomonas maltophilia (noted both in the Copenhagen and Leeds CF centres). But this is not a good reason to fail to eradicate any potential pathogens, symptoms or not, as they appear which is the policy in many European CF centres.

Fig. 29: The 2001 Nutrition Consensus Group at Artimino


5 years influence management. A total of 169 patients (100 female), median age 2.2 years (range 0.3-4.9) were identified. Eleven per cent of patients underwent subsequent management changes, including liver ultrasound, fasting glucose, and a short course of iron. Of particular importance, vitamin A and E concentrations were low in 9% of patients, which prompted an increase in prescribed dose. These results support the recommendations for routine blood tests at annual review in preschool CF children.

This study on Annual Assessments fully justifies the time, expense (and for the patient at times distress) of regular annual reviews of relevant laboratory tests in children with CF.


A low fiber intake is suspected to be an underlying factor in gastrointestinal complaints of people with CF. In this study the overall fiber intake was adequate in the cystic fibrosis population. There was no relation between low fiber intake and gastrointestinal problems in the patients with cystic fibrosis.


Incidence of liver disease (LD) associated with cystic fibrosis (CF) and its clinical characterization still is unsettled. We have assessed prospectively the incidence and risk factors of this complication, and its impact on the clinical course of CF. Between 1980 and 1990, we enrolled 177 CF patients without LD in a systematic clinical, laboratory, ultrasonography screening program of at least a 10-year duration. During a 14-year median follow-up (2,432 patient-years), 48 patients developed LD, with cirrhosis already present in 5. Incidence rate (number of cases per 100 patient-years) was 1.8% (95% confidence interval: 1.3-2.4), with sharp decline after the age of 10 years and higher risk in patients with a history of meconium ileus (incidence rate ratio, 5.5; 2.7-11), male sex (2.5; 1.3-4.9), or severe mutations (2.4; 1.2-4.8) at multivariate analysis.

Incidence of cirrhosis was 4.5% (2.3-7.8) during a median period of 5 years from diagnosis of liver disease. Among the 17 cirrhotic patients, 13 developed portal hypertension, 4 developed esophageal varices, 1 developed liver decompensation. Development of LD did not condition different mortality (death rate ratio, 0.4; 0.1-1.5) or higher incidence of other clinically relevant outcomes. In conclusion, LD is a relatively frequent and early complication of CF, whose detection should be focused at the first life decade in patients with history of meconium ileus, male sex, or severe genotype. Although LD does not condition a different clinical course of CF, in some patients it may progress rapidly and require liver transplantation.

A major study from Carla Colombo of Milan, Europe’s leading authority on CF liver disease.


This study reports the results of quantitative analysis of iliac bone histology in adults with cystic fibrosis (CF) and low bone mineral density (BMD). Twenty patients with CF had bone biopsies taken after double tetracycline labeling. Histomorphometric measurements were made by image analysis, and data were compared with those of healthy control subjects. Cancellous bone area was lower in the patients with CF (p = 0.003), and there was a trend towards a decrease in cancellous bone connectivity. Bone formation rate at tissue level was significantly lower in patients with CF (p = 0.0002). Wall width, representing the amount of bone formed within individual remodeling units, was decreased (p < 0.0001), as was mineralizing perimeter and mineral apposition rate. Analysis of resorption cavities revealed lower cavity area, reconstructed surface lengths, and cavity depths (p < 0.003) in patients with CF, whereas eroded surface area was higher (p = 0.0004). These results demonstrate low cancellous bone volume in adult patients with CF with low BMD, the main cause of which appears to be low bone formation at tissue and cellular level. Osteomalacia was diagnosed in one patient. This condition should be excluded as a cause of low bone mineral density in patients with CF and vitamin D insufficiency corrected.


Treatment of allergic bronchopulmonary aspergillosis with itraconazole is becoming more widespread in chronic lung diseases. A considerable number of patients are concomitantly treated with topical or systemic glucocorticoids for anti-inflammatory effect. As azole compounds inhibit cytochrome P450 enzymes such as CYP3A isoforms, they may compromise the metabolic clearance of glucocorticoids, thereby causing serious adverse effects. A patient with cystic fibrosis is reported who developed iatrogenic Cushing’s syndrome after long-term treatment with daily doses of 800 mg itraconazole and 1,600 microg budesonide. The patient experienced symptoms of striae, moon-face, increased facial hair growth, mood swings, headaches, weight gain, irregular menstruation despite oral contraceptives and increasing insulin requirement for diabetes mellitus. Endocrine investigations revealed total suppression of spontaneous and stimulated plasma cortisol and adrenocorticotropic. Discontinuation of both drugs led to an improvement in clinical symptoms and recovery of the pituitary-adrenal axis after 3 mo. This observation suggests that the metabolic clearance of budesonide was compromised by itraconazole’s inhibition of cytochrome P450 enzymes, especially the CYP3A isoforms, causing an elevation in systemic budesonide
concentration. This provoked a complete suppression of the endogenous adrenal function, as well as iatrogenic Cushing’s syndrome. Patients on combination therapy of itraconazole and budesonide inhalation should be monitored regularly for adrenal insufficiency. This may be the first indicator of increased systemic exogenous steroid concentration, before clinical signs of Cushing’s syndrome emerge.

An important report as Aspergillus is increasingly common and the two drugs are used not infrequently. The occurrence was later investigated further by the Copenhagen team. Suppression of the adrenal glucocorticoid synthesis was observed in 11 of 25 cystic fibrosis patients treated with both itraconazole and budesonide. The pathogenesis is most likely an itraconazole caused increase in systemic budesonide concentration through a reduced/inhibited metabolism leading to inhibition of adrenocorticotrophic hormone secretion along with a direct inhibition of steroidogenesis. In patients treated with this combination, screening for adrenal insufficiency at regular intervals is suggested. [PubMed] There was also a further case report from the UK [PubMed]


A group of patients who harbour the same highly transmissible strain of Pseudomonas aeruginosa were identified at a cystic fibrosis (CF) centre. Isolates of this strain display a number of unusual phenotypic features including resistance to most typical antipseudomonal antibiotics. A study was undertaken to see if there was a difference in treatment requirements between CF patients with chronic infection with their own unique P aeruginosa strains (group 1) and those who harbour a highly transmissible strain (group 2). METHODS: Data on treatment requirements for the year 2000 were collected from the case records of CF patients with chronic P aeruginosa infection who had received inpatient treatment. Patients co-infected with Burkholderia cepacia or other highly transmissible strains of P aeruginosa were excluded. RESULTS: There were 2/56 and 3/22 deaths in groups 1 and 2, respectively; these patients were excluded from the analysis. No difference was found between the two groups for mean age, % predicted forced expiratory volume in 1 second (FEV(1)), % predicted forced vital capacity (FVC), and body mass index. Patients in group 2 had a greater median (range) number of intravenous antibiotic days (60 (17-216) v 33 (4-237) days; p=0.01), inpatient days (39 (7-183) v 16 (1-172) days; p<0.01), and inpatient episodes (3 (1-9) v 2 (1-6) (p=0.05)), and more respiratory exacerbations (average 3-7 days (1-31) v 3-3 (1-32; p=0.01).Patients who harbour the highly transmissible P aeruginosa strain have a greater treatment burden than patients with CF who harbour their own unique strains. These findings support the need for microbiological surveillance for highly transmissible P aeruginosa and the implementation of infection control measures to prevent cross infection.


Estimates of the level of transcripts from the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene required to develop a CF phenotype range from 4-20% of normal. Due to the importance of obtaining reliable data on this issue for therapeutic strategies, we developed a novel polymerase chain reaction-based method to quantify CFTR transcripts and applied it to the analysis of nasal epithelium RNA of five patients with CF and the 3272-26A>G/F508del genotype. We calculated that 8.2 +/- 0.84% of the total CFTR RNA present in these five patients is normal full-length CFTR mRNA. We then demonstrated (in nasal samples from F508del carriers, n = 30) that the abundance of full-length F508del CFTR transcripts is reduced compared with wild-type transcripts, and estimated that the average ratio of F508del/wild-type transcripts is 0.87 +/- 0.06. To determine the reduction of wild-type transcripts relative to normal CFTR individuals, we corrected for the lower abundance of the F508del transcripts and calculated that the five patients with CF have, on average, 4.7 +/- 0.45% of the normal level of wild-type CFTR mRNA. Because these patients have mild CF compared with F508del homozygotes, this CFTR mRNA level appears to be sufficient to avoid the severe complications of the disease.

The question often raised is just how much CFTR activity is required to avoid serious lung involvement. Obviously 50% of normal, as is present in heterozygotes is adequate. Certain patients with mild mutations seem to avoid serious lung involvement. So the present study is reassuring that 5 - 10% which may be achieved with gene therapy may be adequate to have a significant effect.


Digital clubbing is a common sign in cystic fibrosis (CF) and in a variety of other diseases. However, its pathogenesis remains obscure. In diseases other than CF clubbing has been noted after cure of the underlying disease. The aim of this study was to assess whether clubbing is reversible in CF patients after lung transplantation. Digital clubbing was investigated in 3 CF patients, prior to and after lung transplantation. Distal phalangeal depth (DPD) and interphalangeal depth (IPD) of the index finger were measured using a skinfold caliper, and the DPD/IPD ratio was calculated. The mean DPD/IPD ratio was 1.08 +/- 0.05 prior to transplantation and 1.00 +/- 0.06, 0.96 +/- 0.06, 0.92 +/- 0.04, and 0.89 +/- 0.07 at 3, 6, 12, and 24 months after transplantation, respectively. In all 3 patients, the DPD/IPD ratio was greater than 1 before transplantation. In 2 patients, this ratio decreased to less than 1 within 3 months, and in the third patient within 9 months after surgery. The authors conclude that digital clubbing is reversible in CF
The reversal clubbing was noted by some of the people with CF who had the first transplants in the Eighties.


A report of a 20-year-old patient with cystic fibrosis who developed acute nonoliguric renal failure associated with inhaled tobramycin. Clinical evaluation and renal biopsy findings were consistent with aminoglycoside-induced changes. Renal failure due to inhaled aminoglycosides has not been previously reported. The incidence may rise, however, with the increased use of this treatment modality. Measurable tobramycin levels due to inhalational therapy with conventional dosing in the reported patient indicate that the drug can be systemically absorbed, and renal tubular toxicity may occur.

This report is worrying for inhaled tobramycin is now widely used and certainly in the doses used (for example 300mg twice daily) there is definite absorption. Whether this will be harmful in the long term remains to be seen.


The objective was to determine the composition of the Cystic Fibrosis (CF) Population attending specialist UK CF centres in terms of age, gender, age at diagnosis, genotype and ethnicity. With the planned introduction of the national CF screening programme in the UK, cystic fibrosis transmembrane regulator (CFTR) mutations were compared between different ethnic groups enabling a UK-specific frequency of mutations to be defined. Data were analysed from the patient biographies held in the UK CF Database (see www.cystic-fibrosis.org.uk). The UK registered population of 5,274 CF patients is 96.3% Caucasian with a male preponderance that significantly increases with age. The majority of the 196 non-Caucasian CF patients are from the Indian Subcontinent (ISC), of which one in 84 UK CF patients are of Pakistani origin. The commonest CFTR mutation, deltaF508, is found in 74.1% of all CF chromosomes. In the Caucasian CF population, 57.5% are deltaF508 homozygotes but the UK ISC CF population with only 24.7%, has significantly fewer deltaF508 homozygotes patients (95% confidence interval (CI) 0.2-0.4). The distribution of Caucasian patients with deltaF508/deltaF508, deltaF508/Other and Other/Other does not fit the expected distribution with a Hardy-Weinberg model unless those patients without a detected mutation are excluded (P<0.001). The UK CF Database has shown the UK CF population to have distinct characteristics separate from the North American and European CF Registries. The ISC group contains many mutations not recognised by current genetic analysis, and one in four ISC patients have no CFTR mutations identified. The CFTR analysis proposed for the screening programme would detect 96% of patients registered in the database, but is unlikely to achieve the desired >80% detection rates in the ethnic minority groups. Screen-positive, non-Caucasian infants without an identifiable CFTR mutation should be referred for a sweat test and genetic counselling when serum trypsinogen concentrations remain elevated after birth.


Colonisation with Pseudomonas aeruginosa is common in adults with cystic fibrosis (CF) and there is increasing evidence that transmissible strains may cross colonise patients. However, transmission of these strains by social contact to healthy non-CF individuals has not been described. A case is presented where an adult CF patient colonised by an epidemic P. aeruginosa strain infected her parents with subsequent morbidity.


To review 9 years of annual assessment data in cystic fibrosis (CF) and evaluate the frequency of hepatobiliary abnormalities and the correlation between ultrasound and biochemical findings. Over a 9-year period (1990-99), 168 children (age range 1-18 years) with CF have undergone an annual assessment which has included clinical, biochemical and ultrasoundographic evaluation of the hepatobiliary system. We have retrospectively reviewed the sequential ultrasound reports and correlated them with the contemporaneous biochemical results. A total of 725 ultrasound examinations were performed over the review period. Sixty patients had at least one examination showing an abnormality of liver echo texture and in 39 patients this was a persisting finding. Seven patients (4.2%) developed frank cirrhotic change on ultrasound criteria, while 15 patients (8.9%) had evidence of persistent splenomegaly. Gall-bladder calculi were present in 4.8%. In 176 examinations (24%) there was disparity between the ultrasound findings and aspartate aminotransferase (AST) levels. In 3.0% of cases (five patients) there were persisting abnormalities of liver echo texture and persisting splenomegaly with a normal range AST value. The authors concluded no perfect method of assessing hepatobiliary involvement in CF is currently available. Ultrasongraphic and biochemical assessment may reflect different aspects of disease progression. Routine use of ultrasound in annual assessment allows identification of a minority of patients with...
liver changes but with normal biochemistry.


Hypertrophic pulmonary osteoarthropathy (HPOA) may complicate the advanced lung disease that is associated with cystic fibrosis, resulting in severe joint pain and early-morning stiffness. Symptoms are usually controlled with the administration of nonsteroidal anti-inflammatory drugs, physiotherapy, and, on occasions, oral corticosteroids. This report describes a case of refractory HPOA with complete remission following the administration of IV pamidronate, which is a potent inhibitor of osteoclastic bone resorption. Symptom relief resulted for up to 3 months, but repeated courses of pamidronate have been required to maintain symptom control.

This is a practically useful report of a treatment for hypertrophic pulmonary osteoarthropathy where other measures have failed.


Inhaled antibiotics are an established treatment for chronic Pseudomonas aeruginosa (PA) infection in patients with cystic fibrosis (CF). However, inhaled antibiotics might also have prophylactic potential to delay acquisition of PA in early stages of the disease. From 1986-1999, all CF patients at this center who experienced defined risk situations for acquisition of PA (28 patients) received inhaled gentamicin (80 mg BID for those < 12 months; 120 mg BID for those > 12 months) for a minimum of 3 years. Twelve patients had repeated risk situations and continued this prophylaxis without interruption during the entire study period (group 1). In the remaining 16 patients, inhaled antibiotics were discontinued at various times for a variety of reasons (group 2). None of the patients in group 1, but 7 in group 2, became chronically infected with PA (P = 0.01). Lung function and chest X-ray scores were significantly worse in those 7 infected patients, when compared to the non infected ones in both groups. This suggests that long-term-prophylaxis with inhaled gentamicin can effectively delay acquisition of PA and decrease disease progression in children with CF.

This study from Austria appeared to start the years after the first report of eradication of early P. aeruginosa in 1985. The treatment appeared to be very effective in avoiding chronic infection. However, a subsequent study of urinary NAG levels suggested some renal involvement so the gentamicin was stopped.