THE NEW MILLENNIUM CLINICAL 2001


This document was influential in improving care both in the UK and Europe. The principles were similar to those subsequently incorporated in to the ECFS standards of care document in 2005 (Kerem et al. J Cyst Fibros 2005; 4:7-26. below). This UK document was still widely used in 2010 when it was intended to replaced it with a care pathway document. However, the principles of good care remain much the same except the precautions against cross infection with *P. aeruginosa* have become more stringent during the decade as the problems associated with highly transmissible strain of *P. aeruginosa* were recognised (Jones et al. Lancet 2001; 358:557-558.[PubMed]).


Nine children with CF treated with growth hormone had significantly greater height, height velocity, weight, weight velocity and change in lean tissue mass. Also the treated group had significant improvement in forced vital capacity compared with the year before the study, and respiratory muscle strength improved. The number of hospitalizations and outpatient intravenous antibiotic courses significantly decreased in the treated group but did not change in the control group. Results of this before and after study of GH treatment in cystic fibrosis suggested that GH improves growth and clinical status.

There was a later controlled trial by Hardin HS et al. 2006 (below). Also Schnabel D et al. 2007 (below) from Germany. However, most centres do not use and would be unlikely to use growth hormone to treat children with CF; its role is still not entirely clear particularly as the nutritional state of children with CF improves with better treatment.


The repeated need for venous access is a major problem for a significant proportion of children with CF, in some amounting to severe needle phobia. Another simple method of improving their quality of life was to use inhaled nitrous oxide before venepuncture. The technique was already used successfully in Belfast (Mills et al. 2001 below) and subsequently elsewhere for children with CF undergoing painful procedures (Williams V et al. Paediatr Nurse; 2006;18:31-33). [PubMed]

This seemed an excellent form of treatment for children having distressing procedures and is obviously used successfully in a number of CF centres by experienced clinicians (Mills & Redmond, 2001 below). The method is now used in many CF Centres in the UK.


The distress of some children at even the thought of an intravenous injection or insertion of a
interventions in CF.

during infancy and early childhood. These findings have important implications for early
airway function is already diminished soon after diagnosis in infants with CF and does not catch up
and at the second test with 72% of infants having a value less than the fifth percentile. So the
technique. The mean FEV0.5 was significantly lower in infants with CF both shortly after diagnosis
was performed by Ranganathan et al. (Am J Resp Crit Care Med 2004; 169:928-933). [PubMed]
above and subsequent studies). This present study confirms this fact. A follow up study

Some degree of airway obstruction, increased residual volume and hyperinflation from an early
controls, even in those without clinically recognised previous lower respiratory illness.

Stroobant J, Wade A, Wallis C, Stocks J. Airway function in infants newly diagnosed with
In an open cross-over trial, 48 children were allocated in random order to
12 weeks of once-daily rhDNase (2.5 mg), alternate-day rhDNase (2.5 mg),
and twice-daily 5 ml 7% hypertonic saline. The primary outcome was FEV1.
The mean FEV1 increased by 16% (SD 25%), 14% (22%), and 3% (21%)
with daily rhDNase, alternate-day rhDNase, and hypertonic saline
respectively. There was no difference between daily and alternate-day rhDNase. However, daily
rhDNase showed a significantly greater increase in FEV1 than hypertonic saline (8% (2 to 14),
p=0.01).

It is no surprise that hypertonic saline, delivered by jet nebuliser, was not as effective as daily
rhDNase, although there was variation in individual response. Interestingly there was no evidence
of a difference between daily and alternate-day rhDNase. Although inhaled hypertonic saline was
less effective as a mucolytic than rhDNase, it was considerably cheaper. It must be stressed that
these group responses and there is considerable individual variation between patients and it is
important that clinicians assess the individual response of each patient when prescribing these
treatments. Also it was later shown that failure to respond to rhDNase may be related to the

Two further examples, from the Liverpool Adult CF Centre, of a transmissible Liverpool strain of P.
aeruginosa shown to be identical by genotyping, infecting patients in the same clinic. Here it was
shown to have infected patients already chronically infected with another strain of Pseudomonas.
The Liverpool strain (LES strain), was first recognised in the Liverpool paediatric clinic, (Cheng et
al. 1996 [PubMed] above) was identified in a number of other UK CF centres in a subsequent

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In the first study, CF patients born between 1973 and 1981 in North Eastern Italy were split into 4
groups according to the method of diagnosis: screening by meconium test (58 patients);
meconium ileus (45 patients); symptoms and pancreatic insufficiency (PI); (75 patients),
or symptoms and pancreatic sufficiency (PS; 19 patients). The patients were followed for up to 26
years by three CF centres sharing common treatment protocols. In this first study, the patients
very much the same as in the North Eastern Italian study. In a second study, the patients were

Superinfection with a transmissible strain of Pseudomonas aeruginosa in adults

A, Sciuto C, Pardo F, Maguzzu G. Neonatal screening for cystic fibrosis: long-term clinical
detected by newborn screening (PI) showed better survival and nutritional status compared to patients diagnosed through meconium ileus or symptomatic presentation with PI. The PS patients diagnosed by symptoms showed the best outcome as would be expected as most of them had a mild genotype.

In the second study, two cohorts of CF patients born between 1983 and 1992 were compared. Patients from one cohort (126 patients) were born in the Veneto region, where a neonatal screening program had been established based on immunoreactive trypsinogen. Patients from the other cohort (152 patients) were born in Sicily, where an intensive program of early diagnosis by symptoms was implemented. The cohorts were comparable for CF incidence, CFTR genotypes, gender proportion and common treatment protocols. In this second study, the Veneto neonatal screened cohort showed better outcome with regard to survival and nutritional status over 16 years of follow-up.

Observational cohort studies cannot give definitive evidence of the clinical benefit of neonatal CF screening; however, data have been accumulated which strongly suggest a better clinical outcome for CF patients born in an area where a screening program is performed always provided they receive good care after diagnosis. The Italians, in particular astute clinicians such as Gina Mastella, deserve the credit for having pioneered neonatal CF screening in Europe since 1973; he was awarded the Rossi Medal of the European CF Society for his work with cystic fibrosis.


In September 1997, a 25-year-old Italian lady with CF spent 3 weeks in Thailand. In August 1998, her pulmonary function rapidly declined, with productive cough and intermittent fever. The chest x-ray films revealed diffuse, small, patchy opacities in the upper lobes. Burkholderia pseudomallei (BP) were isolated from specimens of the patient’s sputum and were identified by means of 16S rDNA sequencing. The diagnosis of melioidosis was serologically confirmed. Continuous therapy with ceftazidime and co-trimoxazole and maintenance with co-trimoxazole, doxycycline, and chloramphenicol resulted in eradication of Burkholderia pseudomallei.

This infection appears to be a particular risk for the increasing number of adults with CF travelling abroad to places such as Thailand as they seem to be prone to melioidosis. Subsequently further cases were reported. Burkholderia pseudomallei is an important cause of pneumonia and septicaemia in Thailand particularly in the rainy season when it may get into the water supply and there are now almost 70 cases of the infection causing serious illness reported in people with cystic fibrosis. So going on holiday to Thailand represents a definite risk for a person with CF particularly in the rainy season. B. pseudomallei infection has also been reported affecting a person with CF in Brazil (Barth AL et al, 2007. [PubMed] below).


Follow-up of the Wisconsin screened infants showing significantly better long term growth and nutritional state in the screened group.

This particular paper was influential in the eventual recommendation for national neonatal CF screening by the UK Government in May 2001 when Yvette Cooper, the Health Minister at the time, agreed to the introduction of nationwide neonatal CF screening. There had been a major campaign to introduce national neonatal CF screening led by the UK CF Trust since 1996. Previously the Child Health Subgroup of the UK National Screening Committee (NSC) had considered the evidence of long term benefit was insufficient to recommend national neonatal CF screening. A previous paper from Wisconsin (Farrell et al, N Eng J Med 1997; 337:963-969 [PubMed] was considered by Professor NJ Wald, to provide no evidence of any benefits of screening.

Even after the UK Government's decision, following this 2001 paper, the the Child health Group of the National Screening Committee remained unconvinced! As recently as 2002, after the Government had agreed to neonatal CF screening in 2001, Dr David Elliman, Chair of the Child Health Subgroup of the UK National Screening Committee, wrote the National Screening Committee (NSC) concluded that there was currently insufficient evidence of longer term benefit, specifically in relation to pulmonary function, to support implementation of newborn screening and then adds without any comment, subsequently a ministerial decision was made in July 2001 to formally introduce screening in England followed shortly by a similar decision in Scotland” (Elliman DAC, et al. Arch Dis Child 2002; 87:6-9). [PubMed] This view was still held by the NSC in 2005.

Fortunately this 2001 trial from Wisconsin resulted in the agreement of the Health Minister Yvette Cooper and the UK Government and was the culmination of a 7 year, vigorous and at times heated, campaign by the UK CF Trust. The introduction of national neonatal CF screening was undoubtedly one of the major clinical advances, if not the major advance, of the decade in the UK.

Figure 21: Professor Philip M. Farrell (from research.med.wisc.edu/farrell/)

(Farrell et al, N Eng J Med 1997; 337:963-969 [PubMed] was considered by Professor NJ Wald, to provide no evidence of any benefits of screening. The History of Cystic Fibrosis by Dr James Littlewood OBE 3 Copyright © cfmedicine.com 2009-2011)
Phillip Farrell (Fig. 21) is the Professor of Pediatrics and Population Health Sciences at the University of Wisconsin School of Medicine and Public Health and responsible for the Wisconsin neonatal screening programme from 1985. He trained with Paul di Sant'Agnese at the NIH until he moved to Wisconsin in 1977. His work was influential in the introduction of neonatal screening in the UK between 2001 and 2007 and also throughout the United States by 2009.


This was a 96-week, randomized, double-blind, placebo-controlled trial involving 49 CF centers and 474 children aged 6 to 10 years with good respiratory function (FVC 85% predicted). At 96 weeks the treated group had maintained their respiratory function levels with slight treatment benefit for dornase alfa compared with placebo with a 34% reduction in the risk of respiratory tract exacerbations.

The results of this trial influenced some clinicians to try young CF patients on Pulmozyme before they developed chronic infection; this became routine practice in at least one large UK Paediatric CF Centre and also in Copenhagen where the treatment was found to reduce the incidence of new positive respiratory cultures (Frederiksen B et al. Acta Paediatr 2006; 95:1070-1074. [PubMed] below).


Serum concentrations of linoleic acid and docosahexaenoic acid were significantly lower in patients with severe cystic fibrosis transmembrane conductance regulator mutations, such as DF508, suggesting an association between the basic defect and abnormal essential fatty acid metabolism in CF patients. A relationship between these fatty acids and the basic defect had been suggested previously – most recently by Freeman et al, (1999 above).


Of 176 women with CF, 35% were occasionally incontinent of urine but 24% were regularly incontinent. As urine loss is likely to be an under-reported problem, particularly in a CF clinic devoted to mainly chest problems, the authors suggest that women with CF should be asked directly about urinary incontinence as part of their routine follow-up. Pelvic floor muscle exercises were said to help. Also there was a similar report from Manchester Adult CF clinic (Orr A et al. BMJ 2001; 322:1521). [PubMed]

These are really important reports which would improve the recognition of a distressing and relatively common symptom in women with CF which may go unreported and cause considerable distress for many years.


A prospective surveillance study in the Manchester adult CF centre showed 22 (14%) of 154 patients with chronic *P. aeruginosa* had isolates with similar and new pyocin and pulsed-field gel electrophoresis types. Cross-infection by a new multiresistant *P. aeruginosa* strain had therefore occurred. The authors recommended CF centres should undertake microbiological surveillance of their patients.

A subsequent report from Manchester showed that patients infected with this strain of *Pseudomonas* required more intensive treatment (Jones AM et al. Thorax 2002; 57:924-925. below [PubMed]

An important paper by Dr Andy Jones (figure 23), consultant physician at the Manchester Adult CF Centre, that was influential in the eventual introduction of widespread microbiological surveillance of CF centres in the UK. This led to the discovery that cross infection was a common occurrence in many of the large CF centres (Scott & Pitt 2004 below). A similar clinical situation with a transmissible *P. aeruginosa* had been reported from the Liverpool paediatric CF clinic in 1996 (Cheng K et al, 1996 above).
These papers were influential in the introduction of a more rigorous policy of segregation according to microbiological status in most CF centres but in some not without a degree of reluctance on the part of some CF clinicians for example one senior physician wrote - "There is a real risk of stigmatisation by sputum bacteriology, enhanced anxiety about what may be a relatively benign organism (many adults with CF remain well despite positive cultures of Pseudomonas aeruginosa for decades) and fear of attending a CF centre or any school or social event where another person with CF may be met. There are risks in doing too little but it may be worse to do too much. Geddes DM. Lancet 2001; 358:522-523). Also one paediatrician wrote - "This (segregation) means there will be loss of continuity of care as well as flexibility for the families choosing which days they come to see us". One of his paediatric colleagues described those at the UK CF Trust responsible for recommending patient segregation as "an unruly bunch of zealots"!! Fortunately only a minority of clinicians held these views!!


There are few studies evaluating the safety of inhaled steroids in young children. The authors prospectively administered beclomethasone dipropionate (BDP) 420 mcg daily for 2 months to 12 clinically stable young children with CF without affect on urine and blood cortisol levels, adrenal reserve, or increase in airway infection. Also there was a fall in bronchoalveolar lavage fluid inflammatory markers following the inhaled steroid treatment.

This was one of a number of small studies of inhaled corticosteroids in people with cystic fibrosis. Clinical experience shows that a few patients quite obviously do benefit significantly from inhaled steroids particularly young patients with troublesome wheezing and bronchial lability. However, a subsequent UK study of withdrawal of inhaled steroids from people with CF showed many patients were deriving no apparent benefit and their inhaled steroids could be withdrawn without ill effects (Balfour-Lynn et al. 2006 [PubMed] below). Presumably some of these patients would have derived some benefit at the time the steroids were started and there are a minority of children with CF who do derive great benefit from inhaled steroids. However, these patients were not included in Balfour-Lynn’s steroid withdrawal study as, understandably, their doctors (and almost certainly their parents!) were unwilling to stop their steroid treatment.

Also, although some paediatricians who published short term studies on inhaled steroids found it difficult to accept, undoubtedly in some children the rate of growth is affected by taking inhaled steroids in the doses used in this present study this will be detected provided the children are followed up for longer and measured carefully (by no means always the case in busy general paediatric clinics!). Two months is an inadequate time to identify adverse effects on growth (see Littlewood et al, 1988 [PubMed] above for full discussion of the adverse effect of inhaled steroids on growth).


The primary aim of this retrospective study was to establish the incidence and severity of auditory deficit in 70 people with CF. Twelve (17%) displayed hearing loss considered to be caused by repeated exposure to aminoglycosides. There was a nonlinear relationship between the courses of aminoglycoside therapy received and the incidence of hearing loss. The severity of the loss did not appear to be related to the number of courses received. Assuming the risk of loss to be independent for each course, preliminary estimates of per course risk of hearing loss were less than 2%.

Upon comparison with previous clinical studies and experimental work, these findings suggest that the incidence of cochleotoxicity in CF patients is considerably lower than would be expected, even suggesting that the CF condition may confer some protection against aminoglycoside cochleotoxicity. Subsequently increased susceptibility to aminoglycoside toxicity has been related to the possession of a particular gene the mitochondrial 12S rRNA A1555G mutation is one of the important causes of aminoglycoside-induced and nonsyndromic hearing loss (Qian Y, Guan MX. Antimicrobial Agents & Chemotherapy 2009; 53:4612-4618 [PubMed]; Bitner-Glindzicz Met al. Prevalence of mitochondrial 1555A->G mutation in European children. N Engl J Med 2009; 360:640-642). [PubMed]


One of the early studies (the first using tobramycin) confirming that early nebulised antibiotic treatment of airway colonisation with Pseudomonas aeruginosa could delay onset of chronic lung infection in patients with cystic fibrosis. There was successful eradication of the organism in 14 of
15 patients with cystic fibrosis who had been colonised by *P. aeruginosa*. Patients inhaled 80 mg tobramycin twice daily for 12 months. Eradication was confirmed by sequential respiratory cultures and serum antibody titres that were negative for *P. aeruginosa*. The antibiotic therapy regimen maintained pulmonary function at high levels (Further support for Littlewood et al, 1985 [PubMed] above and Valerius et al, 1991above). [PubMed]

It is of interest that a subsequent trial showed that 80 mg of nebulised injectable tobramycin twice daily on a regular basis showed similar benefit to alternate monthly cycles of 300 mg twice daily of tobramycin for inhalation (Nikolaizik WH et al. Can Respir J 2008; 15:259-262 [PubMed]).

Professor Felix Ratjen (figure 24) was head of the CF Centre in Essen Germany until 2005 when he moved to the Hospital for Sick Children in Toronto as Head of Respiratory Medicine to hold the Sellers Chair for Cystic Fibrosis. He is involved in many areas of pediatric respiratory medicine but particularly in cystic fibrosis. Although a scientific researcher into areas of inflammation and respiratory function he is heavily involved in patient care and the introduction of new treatments.


First of two important papers from Rosenfield et al. to assess the serum and lower respiratory tract tobramycin concentrations produced by a single dose of tobramycin for inhalation (TOBI) in patients with CF aged 6 months to 6 years. A 180-mg dose of inhaled tobramycin produced a mean peak serum level of 0.5 microg/ml; a 300-mg dose produced a mean peak serum level of 0.6 microg/ml both well below the accepted maximum trough concentration with parenteral dosing (2 microg/ml). The target epithelial lining fluid level in the lung was 20 microg/ml - 10-fold greater than the minimal inhibitory concentration for most Pseudomonas isolates. The mean epithelial fluid level was 90 microg/ml.

So in patients with CF, aged 6 months to 6 years, even a single 300-mg dose of inhaled tobramycin (TOBI) appeared to produce safe serum concentrations and high drug concentrations in the bactericidal range in the lower respiratory tract. Although it is not known if these serum levels, sustained over many years, are without side effects.


Forty infants from 3 participating sites over a 2-year period had annual bronchoalveolar lavage (BAL) for culture and measurements of pro- and anti-inflammatory cytokines, semi-annual infant pulmonary function testing, and quarterly clinical evaluations. Both the prevalence of CF pathogens and their density in BAL fluid increased with age. Infants had neutrophilic lower airway inflammation and elevated IL-8 concentrations independent of whether CF pathogens were recovered. Total leukocyte and neutrophil densities and IL-8 concentrations increased with density of CF pathogens in BAL fluid, whether the isolated organism was *P. aeruginosa* or another pathogen. IL-10 concentrations were similar in CF subjects and non-CF historical controls. Infants generally had suboptimal growth (low weight and height percentiles) and obstructive lung disease (decreased expiratory flows and air trapping). Subjects from whom CF pathogens were isolated at > 105 cfu/ml had the worst air trapping and lowest Brasfield chest X-ray scores. The authors considered that their findings would provide a foundation for future studies of early intervention in CF lung disease, including antimicrobial and anti-inflammatory therapy.

In these infants, who were recruited from the CF care centres at each of 3 participating sites, there was an alarming frequency of isolation of pathogens from the lower airways. Unfortunately antibiotic prescribing practices were not specified although the values were said merely not to correlate with antibiotic use. Obviously the presence of *S. aureus* in cultures would be related to whether prophylactic anti-staphylococcal antibiotics were used and whether a policy of early eradication of Pseudomonas was practised.

With regard to these patients, by the age of 3 years, no less than 21% of the children had >105 cfu/ml of *P. aeruginosa*, and 39% of any pathogen. The authors considered that carefully conducted randomized controlled trials in very young patients with CF would help to establish the risk–benefit ratio of therapeutic interventions in this important and vulnerable population.

This ultra cautious attitude shows a radically different approach to that recommended in the UK and many European centres where neonatal screening had been routine for many years and early interventions are the rule e.g. long term flucloxacinilin from diagnosis, amoxil with all "colds" and any positive airway cultures even if no positive culture, and early eradication therapy for positive *P. aeruginosa* cultures whether there are symptoms or not etc, etc. (These policies are detailed in the CF Trust consensus documents e.g, Antibiotic Treatment for Cystic Fibrosis. UK CF Trust, 2009). This difference in approach is reflected in the much higher chronic infection rates in young children in the US than in some UK and many European CF centres.
Dr Rosenfeld (Fig. 25) is Medical Director of the Clinical Research Center and also Medical Director of the Pulmonary Function Laboratory at the Seattle Children's Hospital.

The incidence of CF is very low in the Japanese. All three patients initially developed meconium ileus, and hepatobiliary and pancreatic changes became more severe as age increased. None had the DeltaF508 mutation. The authors reviewed 22 Japanese autopsied cases of CF in the literature. They suggested that the high incidence of meconium ileus in Japanese CF patients may relate to a clinically severe phenotype and reflect a different genetic background between Caucasians and Japanese. The incidence of CF in Japanese had been estimated previously at 1:350,000 considering 104 reported cases in 1997 (Yamashiro Y et al, 1997; 24:544-547). [PubMed] Also Nishimori I, Onishi S. Hereditary pancreatitis in Japan: a review of pancreatitis-associated gene mutations.

Dr Anne Munck (figure 26a) is paediatrician specializing in gastroenterology, nutrition and cystic fibrosis at the University Hospital Robert Debre, Paris. She is heavily involved in cystic fibrosis care and research and is also treasurer of the European Cystic Fibrosis Society.

After early eradication treatment of Pseudomonas aeruginosa subsequent serial isolates were characterized by means of molecular methods to determine whether they were genetically related to the initial strain. Initial colonization was eradicated in all 19 patients and 14. Fourteen patients subsequently acquired a new PA strain with a distinct genotypic profile, suggesting a new source of contamination. Five patients had two PA isolates with identical genotypes, suggesting either previous undetected respiratory tract colonization or a persistent environmental source of contamination.

This was a very important, practically very useful and now oft-quoted paper which settled the question as to whether Pseudomonas was eradicated or merely suppressed with initial eradication antibiotic therapy. It showed quite clearly that, in the majority of patients, the Pseudomonas had been eradicated rather than merely being suppressed as recurrences were of a different genotypic profile.

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A prospective, observational cohort study of 56 children from Melbourne. All were identified as having CF by newborn screening during 1990-92 and the study involved each child having an annual bronchial lavage during the first 2 to 3 years of life. Clinical outcome was determined at 7 years of age. P. aeruginosa infection was diagnosed in 24 (43%) children. Four children died before 7 years of age, all of whom had been infected with a multi-resistant, mucoid strain of P. aeruginosa (Armstrong et al, 2002 below). In the survivors, P. aeruginosa infection was associated with significantly increased morbidity as measured by lower National Institutes of Health scores, greater variability in lung function, increased time in the hospital, and higher rates of rhDNase (Pulmozyme) therapy (P <.01)
Despite neonatal CF screening, the acquisition of \textit{P. aeruginosa} was common by 7 years of age in this CF birth cohort and was associated with increased morbidity and mortality. The high incidence of \textit{P. aeruginosa} infection here is presumably a reflection of the fact the children were born between 1990 and 1992 when early eradication therapy was not routine practice outside certain European CF centres. The high prevalence (43%) of chronic \textit{Pseudomonas} infection at 7 years contrasts with the much lower prevalence (of around 4%) at some European centres where early eradication has been the policy for some years. This paper should be read in conjunction with the following paper (Armstrong et al, 2002 below) where the unusual situation at the time is described of a particularly virulent strain of \textit{Pseudomonas} in the clinic that caused the death of 4 children.

Since 1993 a total of 101 living-donor bilateral lung transplants had been performed with acceptable results. Though most recipients were patients with CF who were rapidly deteriorating, the indications for live-donor lung transplantation had been expanded to include some CF patients in a more elective setting, as well as select patients with other end-stage pulmonary diseases. One-year Kaplan-Meier recipient survival is 72%. Seventy-six percent of deaths occur within the first 2 months after transplantation. There has been no donor mortality and 83% had no problems.  
This is a remarkable series which does not appear to have been replicated anywhere else, although there are further publications on the subject from Starnes group reporting further experience (Backhus LM. Et al. J Heart Lung Transpl 2005; 24:2086-90). [PubMed] Eighty-seven transplants were performed on 84 adult recipients from 1993 through 2003 - 76 had cystic fibrosis. Starnes had been publishing on the subject of living donor lung transplants since 1996. The technique has not become popular in the UK.

This study investigated genotypic and phenotypic changes in \textit{P. aeruginosa} from oropharynx (OP) and bronchoalveolar lavage fluid (BALF) in a cohort of 40 children with CF during their first 3 years. A high degree of genotypic variability was identified, and each patient had unique genotypes. Early isolates had a phenotype distinct from those of usual CF isolates: generally they were non-mucoid and antibiotic susceptible. Genotype and phenotype correlated between OP and BALF isolates. As determined by culture, 72.5% of patients demonstrated \textit{P. aeruginosa} during their first 3 years. On the basis of combined culture and serologic results, 97.5% of patients had evidence of infection by age 3 years, which suggests that \textit{P. aeruginosa} infection occurs early in CF and may be intermittent or undetectable by culture.

![Fig. 26. Dr Jane Burns](image)

This very high incidence of \textit{P. aeruginosa} is quite atypical of UK experience. We do not believe that so many young children are chronically infected (Lee et al, 2004 below) this is based on numerous serial throat cultures, cough swabs and \textit{Pseudomonas} antibody levels estimated over years which correlate closely with the degree of respiratory infection (Brett et al, 1986 above). It seems that the longitudinal careful observation of a group of patients often yields important additional information not apparent in even the most sophisticated controlled trials or cross sectional studies.

Dr Jane Burns (Fig. 26) is one of N. America’s leading CF microbiologists. Her basic research focuses on the natural history of CF airway infections including the pathogenesis of chronic infection and bacterial antibiotic resistance. Dr. Burns is closely involved with the CF Foundation-funded Therapeutics Development Network (TDN) of clinical trials in CF. She serves as the director of the TDN Core Microbiology Laboratory that performs thousands of cultures of CF specimens from clinical trials in the US each year.

A total of 106 strains from 78 patients from 49 CF centers in 22 states were studied. Most (89%) were correctly identified by the referring laboratories as \textit{Alcaligenes xylosoxidans}. However, 12 (11%) strains were misidentified; these were found to be \textit{P. aeruginosa} (n = 10), \textit{Stenotrophomonas maltophilia} (n = 1), and \textit{Burkholderia cepacia} (n = 1). Minocycline, imipenem, meropenem, piperacillin, and piperacillin-tazobactam were the most active since 51, 59, 51, 50, and 55% of strains, respectively, were inhibited. High concentrations of colistin (100 and 200 microg/ml) inhibited 92% of strains. Chloramphenicol paired with minocycline and ciprofloxacin paired with either imipenem or meropenem were the most active combinations and inhibited 40 and 32%, respectively, of strains. Selective media and biochemical identification proved to be useful strategies for distinguishing \textit{A. xylosoxidans} from other CF pathogens. Standards for processing CF specimens should be developed, and the optimal method for antimicrobial susceptibility testing of \textit{A. xylosoxidans} should be determined.
One of an increasing number of pathogens isolated from people with CF.

The authors audited prospectively 322 cough swabs taken from cystic fibrosis children and compared cough swabs with concomitant sputum samples in 30 expectorating patients. A positive cough swab is a strong predictor of sputum culture. However, a negative cough swab does not rule out infection. Persistent symptoms should be further investigated.

A practically useful study as cough swabs are widely used to monitor respiratory pathogens in children with CF in the UK.

Infection with Burkholderia cepacia complex in patients with cystic fibrosis (CF) results in highly variable clinical outcomes. The purpose of this study was to determine if there are genomovar-specific disparities in transmission and disease severity. B. cepacia complex was recovered from 62 patients with CF on > or =1 occasions (genomovar III, 46 patients; genomovar II [B. multivorans], 19 patients; genomovar IV [B. stabilis], 1 patient; genomovar V [B. vietnamiensis], 1 patient; and an unclassified B. cepacia complex strain, 1 patient). Patient-to-patient spread was observed with B. cepacia genomovar III, but not with B. multivorans. Genomovar III strains replaced B. multivorans in 6 patients. Genomovar III strains were also associated with a poor clinical course and high mortality. Infection control practices should be designed with knowledge about B. cepacia complex genomovar status; patients infected with transmissible genomovar III strains should not be cohorted with patients infected with B. multivorans and other B. cepacia genomovars.

An important paper for the management of people with CF who are infected with organisms in the B cepacia complex from experts in this area. Dr Mahenthiralingam is now in Cardiff University in the UK.

Pa acquisition is associated with declining pulmonary status in children with CF, and that this effect is probably gradual rather than precipitous. Because these patients were diagnosed and treated aggressively, our estimates of the effects of Pa acquisition are conservative. The authors conclude that the WCXR appears to be more sensitive than FEV1/FVC in detecting early changes in lung disease associated with CF. Further details in the abstract.

Two hundred forty-eight retail "ready-to-eat" foodstuffs in eight food categories and 134 waters categorized into nine types were analyzed for the presence of the Burkholderia cepacia complex of organisms. Of these, 14 of 26 (53.8%) samples of raw unpasteurized bovine milk were positive for this organism. Consumption of raw unpasteurized milk may therefore act as a potential source of infection with this organism, which is of particular concern for patients with cystic fibrosis, where colonization and infection with this organism can lead to a fatal necrotizing pneumonia and premature death. In addition to the associated risk of infection from fecal pathogens, patients with cystic fibrosis should therefore avoid the consumption of raw unpasteurized milk to minimize the risk of becoming infected with this organism.

Of practical importance as unpasteurised milk is still available.

Five patients with CF with stop mutations and five CF control subjects were treated with parenteral gentamicin for 1 wk, and underwent repeated in vivo measures of CFTR function (nasal potential difference [PD] measurements and sweat chloride [Cl(-)] testing). Results suggest that gentamicin treatment can suppress premature stop mutations in airway cells from patients with CF, and produce small increases in CFTR Cl(-) conductance (as measured by the nasal PD) in vivo.

Between 1985--1989 infants, born in Wales and the West Midlands were randomized to newborn CF screening by heel-prick immuno-reactive trypsin (IRT) measurement or diagnosis by clinical presentation. Eligible children with CF who died in the first 5 years of life were identified from the local pediatricians and from the National UK CF Survey. In all, 230,076 infants were randomized to be screened, while 234,510 were unscreened. One hundred seventy-six CF children were identified, of whom 7 died in the first 5 years of life, 3 having presented with meconium ileus. Median age of diagnosis in the screened group was 8 weeks. On an intention to treat analysis, all 4 non meconium ileus-related deaths occurred in the unscreened group (Fisher's exact test, P <
The clinical presentation of 2 of these infants led to them being diagnosed prior to 8 weeks, i.e., earlier than would have been likely by screening. In conclusion, newborn screening has the potential to decrease infant CF deaths, but if it is to be successful, identification and treatment must occur as soon as possible after birth.

This the last report of data from the Wales West Midlands neonatal CF screening study funded by the CF Trust. The lessons from this study were that neonatal screening is of no advantage if the diagnosis of the infants is delayed and also if they do not also receive CF centre care.

2001 Cunningham S. Prasad A. Collyer L. Carr S. Lynn IB. Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child 2001; 84:432-433. [PubMed] Nebulised colistin significantly reduced FEV(1), MEF(25%), and SaO(2) for 15 minutes. In 20 children the reduction was greater than 10% from baseline FEV(1), and was still at that level in five at 30 minutes.

By this time colistin was the most widely used inhaled antibiotic in the UK both for early eradication of P aeruginosa and for chronic suppressive therapy. Pre treatment assessment was recommended.

2001 Saglani S. Bush A. Cystic fibrosis and Down's syndrome: not always a poor prognosis. Pediatr Pulmonol 2001; 31:321-322. [PubMed] A child developed a bronchiolitis-like illness and was found to have mosaic Down’s syndrome (diagnosed on karyotype) and also cystic fibrosis, diagnosed on the basis of a high sweat osmolality (247 mosmoles/kg sweat; normal, 62-137) and a homozygous delta F508 genotype. Despite two potentially life-threatening conditions, the child is doing well at the age of 7 years, despite pancreatic insufficient.

2001 Haworth CS. Selby PL. Adams JE. Mawer EB. Horrocks AW. Webb AK. Effect of intravenous pamidronate on bone mineral density in adults with cystic fibrosis. Thorax 2001; 56:314-316. [PubMed] The aim of this study was to assess the effect of intravenous pamidronate on BMD in these subjects. Intravenous pamidronate increases axial BMD in adults with cystic fibrosis, but the high incidence of bone pain associated with this treatment might limit its use.

2001 Sood N. Paradowski LJ. Yankaskas JR. Outcomes of intensive care unit care in adults with cystic fibrosis. Am J Resp Crit Care 2001; 163:335-338. [PubMed] Mechanical ventilation has been discouraged in CF because of poor outcomes, but improved survival and the availability of lung transplantation have increased the indications for care of CF patients in the intensive care unit (ICU). We studied the outcomes of all CF patients admitted to the University of North Carolina Hospitals Medical ICU from January 1990 through December 1998. Seventy-six patients, ranging in ages from 17 to 45 yr (mean: 27 yr), and of whom 53% were female, had 136 admissions for exacerbations of CF with respiratory failure (RF, n = 65), haemoptysis (n = 33), antibiotic desensitization (n = 30), pneumothorax (n = 3), or other reasons (n = 5). Eighty-six percent of the patients with haemoptysis and all of those with desensitization and pneumothorax were alive 1 yr after ICU discharge. Of the 42 patients with RF, 37 (88%) required assisted ventilation. Twenty-three (55%) of the patients with RF survived to ICU discharge and 19 (45%) died. Seventeen (40%) of the patients with RF received lung transplants and 14 were alive 1 yr later. Without transplantation, three (7%) of the patients with RF were alive and three (7%) were dead 1 yr later. Sex, body mass index, and respiratory bacteria did not correlate with survival. We conclude that ICU care for adults with CF who have reversible complications is appropriate and effective. Ventilatory support is appropriate for some transplant candidates.

This is a useful indication of the fate of people with CF admitted to an ICU in a major CF Centre at the present time. Undoubtedly the policy of not admitting to an ICU or ventilating people with CF in no longer valid.

2001 Goldman A. Labrum R. Claustres M. Desgeorges M. Guittard C. Wallace A. Ramsay M. The molecular basis of cystic fibrosis in South Africa. Clin Genet 2001; 59:37-41. [PubMed]. The spectrum of CFTR mutations in three South African populations is presented. To date, a total of 192 white patients (384 chromosomes) with confirmed CF have been tested. deltaF508 accounts for 76% of the CF chromosomes in this group, with 3272-26A-->G, 394delTT and G542X occurring at the following frequencies: 4, 3.6 and 1.3%, respectively. A further 11 mutations account for 6% of CF chromosomes. A total of 91% of the CF-causing mutations can now be detected in the South African white population. Haplotype analysis suggests a founder effect in South Africans of European origin for the two common CFTR mutations, 3272-26A-->G and 394delTT. The diagnosis of CF has been confirmed in 14 coloured and 12 black CF patients. In the coloured population, both the deltaF508 and 3120 + 1G-->A mutations occur at appreciable frequencies of 43 and 29%, respectively. In the black population, the most common CF-causing mutation, the 3120 + 1G-->A mutation, occurs at an estimated frequency of 46%. Four other mutations have been detected, resulting in the identification of a total of 62.5% of mutations in this population.

An interesting paper from Michelle Ramsay’s department in South Africa documenting the mutations found in the coloured and black populations.

Three cases of clinical riboflavin deficiency are reported in children aged 2-10 years attending a regional Cystic Fibrosis clinic. Riboflavin deficiency presented as angular stomatitis in all three patients. Patients were confirmed to be riboflavin deficient by assaying the activity of erythrocyte glutathione reductase. Patients were not on routine supplements of water-soluble vitamins before presentation and were treated with riboflavin supplements as part of a water-soluble vitamin complex. At presentation, one patient had poor nutritional status, but two patients were adequately nourished, receiving overnight Gastrostomy feeds. Data on these two patients indicate an adequate dietary intake of riboflavin, suggesting a mechanism for increased requirements, inadequate absorption or utilization. Additional deficiencies of thiamin, pyridoxine and iron were also observed. This paper reports the occurrence of a vitamin deficiency not previously reported in the cystic fibrosis population.