ORIGINAL ARTICLES

Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period

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Abstract

All newborn infants in East Anglia are screened for cystic fibrosis by blood immunoreactive trypsin assay at 7 days. Thirty eight infants with cystic fibrosis were randomised to treatment with either continuous oral flucloxacillin 250 mg/day (group P, n=18) or with episodic antimicrobials as clinically indicated (group E, n=20). Their progress was monitored from diagnosis to 24 months by a nurse coordinator who visited all infants regularly, at home and in hospital, to collect anthropometric, dietary, clinical, and microbiological data. Mean (range) age of confirmation of diagnosis was 5·7 weeks (1–14 weeks). There was no significant difference in birth weight, genotype, immunoreactive trypsin concentration, neonatal history, symptoms at diagnosis, pancreatic enzyme supplementation, or parental smoking history between the groups. Infants in group E had more frequent cough and a greater number of *Staphylococcus aureus* isolates than infants in group P. More infants of group E were admitted to hospital, had higher admission rates during the second year (19 *v* 5), for longer periods (6·4 *v* 2·2 days), despite receiving more than double the number of courses of antibiotics than group P infants (in addition to flucloxacillin). Continuous prophylactic flucloxacillin from early diagnosis of cystic fibrosis is associated with improved clinical progress during the first two years of life.

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With the development of methods to identify infants with cystic fibrosis during the neonatal period[1] opportunities to intervene early in the course of the disease have become available.

The criteria by which the value of a screening programme may be judged require (i) that the disease is an important health problem for the individual and the community, (ii) that its natural history is known, (iii) that it has a latent or asymptomatic phase, (iv) that it may be identified by a suitable screening test, (v) that facilities for diagnosis and treatment are available, and (vi) that its natural history may be favourably modified by early treatment, which (vii) is acceptable and cost effective.[2]

With respect to cystic fibrosis, criteria (i), (iii), (iv), and (v) have been fulfilled: the prevalence of cystic fibrosis in the UK is about 5000,[3] the disease is often not recognised until well into childhood,[4] it may be accurately identified by neonatal immunoreactive trypsin screening and sweat test,[1] and facilities for its treatment are widely available. The aim of this study was to address criteria (ii), (vi), and (vii).

Since 1981 all infants born in East Anglia have been screened by blood immunoreactive trypsin assay. We reported the incidence, clinical presentation, biochemical and genotypic characteristics, and early natural history of cystic fibrosis in these children elsewhere.[5] In this paper we describe the effects of continuous prophylactic antibiotic treatment on the clinical progress of infants born with cystic fibrosis between 1985 and 1990.

Subjects and methods

Forty two infants with cystic fibrosis born in East Anglia from a population of neonates identified by screening between April 1985 and November 1989 were studied. The diagnosis of cystic fibrosis was confirmed by clinical examination and sweat testing, as described elsewhere.[5]

After confirmation of diagnosis the parents of each affected child were counselled by the nurse coordinator (KN) who conferred with the local paediatrician and family doctor about clinical management, genetic counselling, and follow up.[6] With the consent of parents and the approval of the local ethical committees, infants were enrolled in a prospective control trial. Each was randomly assigned to one of two treatment groups.

Eighteen children received continuous prophylactic flucloxacillin 250 mg/day by mouth in divided doses (group P). Twenty children received episodic antimicrobial treatment when clinically indicated at the discretion of their paediatrician and general practitioner (group E). Four infants withdrew from the study soon after diagnosis for personal and/or domestic reasons, leaving 38 subjects who were followed up to two years.

All infants received chest physiotherapy, pancreatic enzymes, and vitamin supplementation from diagnosis. Choice of feeds was at the discretion of the parents and paediatrician concerned. All infants received a full course of immunisations.

Each child was seen at regular intervals, at home and in hospital, by the full time nurse coordinator, for the collection of domestic, social, nutritional, biochemical, microbiological, radiological, clinical, and anthropometric data. She was continuously available for telephone consultation, to provide parental support, and to coordinate medical and other services.[6]

ANTHROPOMETRY

Body weight was measured using an electronic balance accurate to 5 g. Body length was measured using a stadiometer accurate to 1 mm. The average values for all children of the group, derived from the individual growth curves of each child, taking into account missing data, were used in the analysis. Body weight and length were expressed as SD or z scores based on growth standards derived from normal infants and children born in the Cambridge area.[7]

MICROBIOLOGY

Nose and throat swabs and faecal samples were obtained at regular intervals, and more frequently when the child was unwell, for bacteriological and virological analysis. Respiratory specimens were cultured using standard techniques with emphasis on the identification of *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, and *Pseudomonas aeruginosa*. Stool specimens were cultured on pseudomonas isolation agar after enrichment in acetamide broth.[8] Standard tissue culture methods were used for virus identification. Electron microscopy of faecal samples was undertaken at the Public Health Laboratory, Ashford, Kent. The number of courses of antibiotics, of at least five days' duration prescribed to children in addition to the flucloxacillin received continuously by group P, was recorded.

RADIOLOGY

Radiographs of the chest were taken at 1 and at 2 years of age at the hospital regularly attended by each child. They were assessed by one radiologist (AEWD) using the Chrispin-Norman score[9] and the radiological component of the Shwachman score.[10]

Results

NEONATAL, CLINICAL, BIOCHEMICAL, GENETIC, SOCIAL, AND NUTRITIONAL DATA

The characteristics of the two groups of children, randomised to receive either continuous flucloxacillin (group P) or episodic antibiotics (group E) are shown in table 1. There was no significant difference in their birth weights, gestational ages, or sex distributions. All were detected by neonatal immunoreactive trypsin screening: there was no significant difference in mean blood immunoreactive trypsin concentrations measured at 7 days and at 4 weeks. There was no significant difference in the distribution of genotypes between the two groups. Mean (SD) age of diagnostic sweat test was 7 (3) weeks in group P and 5 (3) weeks in group E (not significant). There were no significant differences in mean sweat osmolalities or sodium concentrations between the two groups. At the time of diagnosis 72% of infants in group P and 60% of infants of group E had symptoms.

Table 1 Characteristics of infants studied

	Group P (n=18)	*Group E (n=20)*
Sex (M/F)	10/8	10/10
Mean (SE) birth weight (g)	3240 (510)	3360 (380)
Mean (SE) gestation (weeks)	39 (1)	39 (1)
Genotype (delta F508)	δδ14, δ4	δδ13, δ7
Mode of presentation: No (%)		
Screening alone	13 (72)	12 (60)
Meconium ileus	2 (11)	6 (30)
Clinical	3 (17)	2 (10)
Blood immunoreactive trypsin (IRT, μg/l)		
Mean (SE) IRT 1	116 (10)	121 (9)
Mean (SE) IRT 2	121 (9)	108 (9)
Sweat test		
Mean (SE) osmolality (mmol/kg)	252 (20)	254 (18)
Mean (SE) sodium (mmol/l)	96 (13)	100 (14)
Symptoms at diagnostic sweat test: No (%)		
Respiratory	7 (39)	5 (25)
Gastrointestinal	2 (11)	2 (10)
Respiratory + gastrointestinal	4 (22)	5 (25)
None	5 (28)	8 (40)

The parents of 34 (89%) infants were married or enjoyed stable relationships. Four infants were born of single mothers into one parent families. The mean (SD) age of mothers of group P was 28·4 (4·9) years, and of fathers was 31·6 (6·6) years. The mean age of mothers of group E was 27·8 (5·7) years, and of fathers was 29·2 (5·5) years. The social class distribution was equal between the two groups. Cigarettes were smoked in 22% of households (n=4) of group P (mean of 5 cigarettes/day) and in 33% of households (n=6) in group E (mean of 8 cigarettes/day); this difference was not significant.

The proportion of infants breast fed at diagnosis was 53% of group P and 16% of group E, and at six months was 7% and 0% respectively. Mixed feeding began within six months in all children and by 12 months 100% of infants were fully weaned to a solid diet. Pancreatic enzyme supplements were taken by all children from diagnosis.

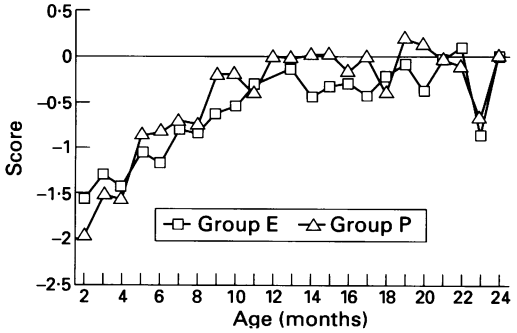

Figure 1 SD (z) scores of weight for age of subjects followed up from birth to 24 months.

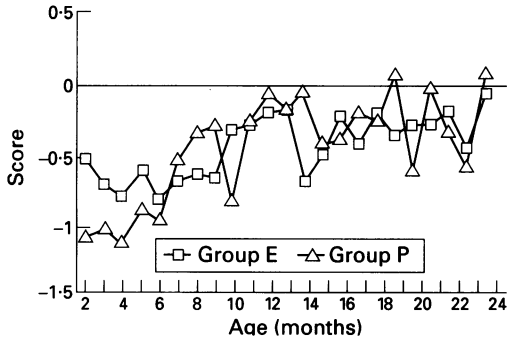

Figure 2 SD (z) scores of length for age of subjects followed up from birth to 24 months.

ANTHROPOMETRY

Figure 1 shows the changes in weight for age z scores at monthly intervals from diagnosis to two years. Starting with z scores of between 1·5 and 2 SDs below the mean at diagnosis, the weights for age of both groups of infants reached within 0·5 SD of the mean by one year. Figure 2 shows the length for age z scores which increased from below −0·5 SD at birth to above −0·5 SD during the second year. There was no significant difference in the growth curves between the two groups.

MICROBIOLOGY

The rate of isolation of bacteria from the respiratory and gastrointestinal tracts of children in the two groups are shown in table 2. Specimens positive for *S aureus* were obtained from the upper respiratory tract of 12 children of group E (60%) during 32 infant months compared with positive specimens from three children (17%) of group P during six infant months ($p<0·01$).

P aeruginosa was isolated from four (22%) children in group P; from the upper respiratory tract on three (1%) infant months (from two (11%) children); from the stools on 22 (10%) infant months (from four (22%) children), and from two children out of four isolation was from both stool and respiratory tract.

P aeruginosa was isolated from the upper-respiratory tract of the children in group E on 10 (4%) infant months (from six (33%) children), and from the stools on 23 (8%) infant months (from six (33%) children). In 3/9 children specimens from both upper respiratory tract and stool were positive, in three from the respiratory tract only, and in three from the stool only. The difference in isolation rates of *P aeruginosa* from the upper respiratory tract between the two groups was not significant ($p<0·1$).

H influenzae was isolated from seven infants (39%) of group P in 10 (5%) infant months.

Table 2 Rate of isolation of bacteria from the upper respiratory and gastrointestinal tracts

			% Months specimens positive				
		% Months specimens	S aureus	P aeruginosa		H influenzae	S pneumoniae
Group	No	obtained		Respiratory tract	Faeces		
P	18	66	2	1	10	5	8
E	20	69	12	4	8	9	9

Table 3 Courses of oral antibiotics taken by children

	Group P (year)		Group E (year)	
Antibiotic	1st	2nd	1st	2nd
Flucloxacillin or cloxacillin	9	8	43	16
Ampicillin or amoxycillin	23	20	38	34
Co-amoxiclav	18	19	26	27
Ampicillin and flucloxacillin	1	0	16	30
Penicillin	2	1	1	4
Erythromycin	3	15	20	27
Co-trimoxazole	10	5	7	18
Cephalosporins	1	1	15	8
Ciprofloxacin	0	0	0	1
Total	67	69	166	165
Courses/child	3·7	3·8	8·3	8·3

From the children of group E *A influenzae* was isolated in 25 (10%) infant months, from 10 (50%) of the children. The difference between these two isolation rates was not significant.

S pneumoniae was isolated from six children (33%) of group P in 18 (8%) infant months, and from 10 (50%) children of group E in 25 (9%) infant months. There was no significant difference in these isolation rates.

Viruses isolated from the respiratory tract included respiratory syncytial virus, adenovirus, Coxsackie A and B, influenza types A and B, and parainfluenza type 3. There was no significant difference in the isolation rates between the two groups.

ANTIMICROBIAL TREATMENT

Children of group E received an average of 8·3 courses of antibiotics per year, and those in group P an average of 3·7 courses per year. The range of antimicrobial agents prescribed is shown in table 3. The courses of flucloxacillin received by children of group P represent a doubling of the dose of this antibiotic.

HOSPITAL ADMISSIONS

The frequency and duration of hospital admissions was lower in the infants and children who received continuous prophylactic antibiotics (group P) than in those who received them episodically (group E) (table 4). The total number of admissions for group P was 23, and for group E was 40 ($p<0·01$). This difference was largely in the second year of life, when there were only five child admissions (five children) in group P compared with 19 child admissions (12 children) in group E ($p<0·01$). The mean (SE) duration of admission of these children during the first year was not significantly different, but in the second year those children receiving continu-

Table 4 Frequency and duration of hospital admissions

	Group P	Group E	p Value
Frequency of admissions*			
Both years	23 (13)	40 (16)	<0·01
First year	18 (9)	21 (11)	NS
Second year	5 (5)	19 (12)	<0·01
Mean (SE) duration of admissions			
Both years	7·3 (1·2)	10·1 (2·2)	NS
First year	8·7 (1·3)	13·4 (4·0)	NS
Second year	2·2 (0·9)	6·4 (0·9)	<0·01

*Frequency of admissions=number of admissions×number of children admitted (in parentheses).

Table 5 Chrispin-Norman and Shwachman x ray scores

Score	Group P (year)		Group E (year)	
	1st	*2nd*	*1st*	*2nd*
Chrispin-Norman				
Median	0	0	0	0
Mode	0	0	0	0
Minimum	0	0	0	0
Maximum	6	4	2	6
Shwachman				
Median	25	23	24	20
Mode	25	25	25	25
Minimum	15	15	20	10
Maximum	25	25	25	25

ous flucloxacillin were admitted to hospital for a shorter duration (mean (SE) 2·2 (0·9) days for group P and 6·4 (0·9) days for group E; $p<0·01$).

In over 80% of cases the reason for admission was for respiratory disease. One child of group E spent 150 days in hospital with respiratory infections (123 days during the first year and 27 days during the second). When he was excluded from the analysis the significance of the difference in hospital admission rates (table 4) remained unchanged. There was no significant relation between a neonatal history of meconium ileus and hospital admission rate; overall those children who had had meconium ileus were admitted to hospital with equal frequency and duration as those who were diagnosed by screening alone. The differences remained significant when between-group differences in smoking and breast feeding were allowed for.

CLINICAL PROGRESS

The appetites, bowel habits, prevalence of respiratory signs (wheeze, rhonchi, and rib recession) were similar between the two groups at all ages. However, cough was commoner in children of group E than group P from six months, and was significantly so from 18 months onwards ($p<0·01$).

RADIOLOGY

The results are shown in table 5. The majority of children in both groups had normal chest radiographs (Chrispin-Norman score 0, Shwachman score 25) at 1 and at 2 years of age, and there were no significant differences between the groups, nor when scores were compared within groups over time.

Discussion

In an earlier paper we reported the incidence, clinical presentation, biochemical and genotypic characteristics of 107 infants born in East Anglia between 1981 and 1990.[5] Both that and this study were made possible by the neonatal immunoreactive trypsin screening programme.[1] We describe here the natural history of cystic fibrosis in 38 infants born since 1985, and show that children who receive continuous oral flucloxacillin from diagnosis are less likely to become colonised with *S aureus*, have fewer respiratory symptoms, and are less likely to be admitted to hospital than those who receive antibiotics as required at the discretion of their doctors.

Population screening of newborns for cystic fibrosis has become established in several parts of the world.[1 4 11] Retrospective studies have suggested that early diagnosis, and therefore treatment, is beneficial in the long term.[4 12 13] However, the conclusions of these studies have been clouded by changes in treatment during the study period, the lack of proper control groups, and their retrospective design. In a prospective study that compared the outcome of infants identified by screening with those who presented later clinically,[14] subjects were not properly matched for duration of treatment.

In the randomised, prospective, intervention study reported here we have shown that the natural history of cystic fibrosis may be favourably modified by early treatment, which is acceptable and cost effective, and in so doing that the criteria that justify the implementation of the screening programme[2] have been fully met.

NEONATAL, CLINICAL, BIOCHEMICAL, AND GENETIC DATA

There were no significant differences in the neonatal characteristics of the two groups (table 1). The distribution of the sexes, gestational ages, birth weights, and genotypes between the two groups was similar. There was a greater number of infants with meconium ileus in group E. However, immunoreactive trypsin screening alone identified 72% of infants of group P and 60% of those of group E. The mean age of sweat test was similar in the two groups, and at diagnosis greater than 60% of infants had symptoms. We have discussed the significance of these data, which do not differ significantly from those of other workers,[10 12 15] elsewhere.[5]

SOCIAL AND DOMESTIC DATA

There were no significant differences in the social and domestic circumstances of the families of the two groups, and both received equal support from the nurse coordinator.

NUTRITION, FEEDING, AND ANTHROPOMETRY

Although there were differences in the choice of feeding in early infancy, by six months all infants were receiving a mixed diet, and by one year all were fully weaned to a solid diet.

We took advantage of modern, locally collected growth standards to compare the growth performance of infants with cystic fibrosis with healthy controls.[7] The weight growth of the children in the two groups with cystic fibrosis was comparable: both showed an increase in weight for age z scores from between $-1·5$ and -2 at diagnosis to close to 0 by 12 months. The overall pattern of growth of both groups was similar to that reported elsewhere.[16] The variation over time between some of the points in the height for age z scores is an indication of the difficulties of measuring body length

accurately in wriggling toddlers, bearing in mind that a z score of 0·5 SD at 12 months represents 1·5 cm, and repeatability of measurements is around ±0·5 cm.

MICROBIOLOGY

The results show a significant reduction, when prophylactic flucloxacillin is given, in both the number of children colonised and in the number of months in which *S aureus* was isolated. No flucloxacillin resistant strains of this organism were isolated, and no child receiving continuous treatment developed candidiasis.

There was a positive association between prior or concurrent carriage of *S aureus* and colonisation with *P aeruginosa* in patients in group E. Such a pattern has been described in another prospective study.[17] Colonisation of the respiratory tract with *S aureus*, which produces a range of cytotoxins,[18] causes epithelial damage enabling pseudomonas to adhere more easily. Additionally, staphylococcal toxins may also inhibit the action of leucocytes further lowering the patient's ability to resist colonisation of the respiratory tract.[16] It has also been suggested that viral infection, particularly with respiratory syncytial virus, may predispose to pseudomonas colonisation. Our study does not support this, there being no significant difference in the number or types of viruses isolated from the two groups. Whatever the mechanism, however, it appears that regular oral flucloxacillin while preventing staphylococcal carriage may also inhibit colonisation with *P aeruginosa*, a major determinant of chronic lung disease in cystic fibrosis.[19]

ANTIMICROBIAL TREATMENT

Although all children in group P received continuous oral flucloxacillin, many from both groups received, in addition from their family doctors, other antibiotics for respiratory infections (table 3). However, children of group E received more than double the number of courses of antibiotics. Those prescribed most frequently were penicillinase resistant or broad spectrum penicillins (flucloxacillin or cloxacillin, ampicillin, amoxycillin, or co-amoxiclav).

HOSPITAL ADMISSIONS

Both frequency and duration of admissions were lower in those children who received continuous flucloxacillin, compared with children in group E who received antibiotics episodically for an average of 12% of the year. In over 80% of cases admissions were for respiratory infections, and even taking into account two children in group E who had more than four admissions each during the study period (one for a total of 150 days), there was a statistically significant advantage in receiving prophylactic antibiotics.

Blood spot screening has been shown to be cost effective,[20] and early diagnosis of cystic fibrosis is associated with a reduced hospitalisation rate in the first two years of life,[12 13] but this is the first time that the advantage of a specific intervention, made possible by neonatal screening, has been demonstrated. In East Anglia, where the average cost of a day in hospital is around £200, and of one day of oral flucloxacillin is 33p, such a reduction in hospital admission rate has large economic as well as medical benefits.

CLINICAL PROGRESS AND RADIOLOGY

The higher frequency of cough in the children who did not receive continuous flucloxacillin (group E) is in accordance with their lower hospital admission rate and staphylococcal isolation rate. However, this was not reflected in the radiology. The absence of a significant difference in chest *x* ray scores between the two groups, and with advancing age, may be explained in two ways. Chest radiographs are an insensitive way of detecting gradually deteriorating pulmonary function, and all scores were done on radiographs obtained when children were well and out of hospital.

CONCLUSION

Identification of infants with cystic fibrosis soon after birth offers the opportunity of optimising treatment, of anticipating potential problems, and of counselling families about further pregnancies. A full time nurse co-ordinator was continuously available to advise the parents of affected children, and her support was greatly appreciated by all families.[6] The impact of the unexpected news of the diagnosis of a chronic disease requiring life long care may be considerably reduced with the availability of expert advice and treatment,[21] particularly during the period when the diagnosis is being established.[22] Counselling and support of parents immediately at diagnosis and for the first year thereafter should be an integral part of any neonatal screening programme.

Nutritional deficits are present from an early age[23 24] and chest infection leads to deteriorating respiratory function.[18] Interventions therefore should be aimed primarily at ensuring optimal nutrition and preventing pulmonary infection. We have shown that close monitoring and support, with commencement of pancreatic enzyme supplements and physiotherapy from diagnosis, is associated with a return to normal growth centiles by 1 year of age. In addition, continuous oral flucloxacillin treatment is associated with fewer hospital admissions, less clinical morbidity, and lower rates of *S aureus* isolation than in children who do not receive such antibiotic prophylaxis.

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