Cystic fibrosis in the United Kingdom 1977-85: an improving picture

British Paediatric Association Working Party on Cystic Fibrosis

Abstract

A national survey was conducted of patients with cystic fibrosis who were known to paediatricians, chest physicians, and others or whose deaths were reported through the death certification authorities in the United Kingdom during 1977 to 1985. From this population based study a revised incidence figure of one affected baby in 2500 live births was produced. Mortality was very high in the first year of life (7·6%) and was substantially greater for females than for males under age 20 years.

A temporal improvement in mortality was found during the period under study, with about 100 more births than deaths occurring each year. This improvement was notable in the first five years of life. Meconium ileus, which used to be a primary cause of early mortality, is becoming increasingly rare as a cause of death. The total prevalence of cystic fibrosis in the UK in mid-1985 was estimated to be about 5000.

Introduction

Survival among patients with cystic fibrosis has steadily improved over the past 30 years.[1] The reasons for this probably include earlier diagnosis and better treatment, but the relative importance of different aspects of management and diagnosis is uncertain. Differences between survival rates reported from different countries and between different clinical centres are considerable,[2,3] and there is evidence that treatment at a recognised cystic fibrosis centre is a primary factor determining life expectancy,[2-4] although because of possible selection bias such reports should be interpreted with great caution.

In 1982 the British Paediatric Association set up a working party on cystic fibrosis in the United Kingdom to advise on whether special centres for patients should be established. The working party undertook a survey in 1983 to try to identify all patients with cystic fibrosis in the UK. The data from that survey were checked and extended in a follow up survey in 1985-6 in which data from death certification were incorporated. This paper reports some of the results of these surveys.

Methods

DATA COLLECTION

In 1983 a questionnaire was sent to all consultant members of the British Paediatric Association, the British Thoracic Society, and the British Association of Paediatric Surgeons in the UK inquiring about patients who were or who had been under their care within the preceding five years. The survey was publicised in the medical press and in *Cystic Fibrosis News* (a magazine sent to anyone who is interested in cystic fibrosis, including patients and parents of patients) inviting people to send information.

In November 1985 all the physicians who had responded to the first survey were sent details of the information held on file for their patients and requested to correct errors or omissions as of 30 September 1985. For patients who had not previously been reported on, the date of diagnosis and, where relevant, immediate cause of death were requested. Further requests for information went to newly appointed consultants and to those who did not respond to the first survey. Information was also provided by the UK Association of Cystic Fibrosis Adults. The box shows what information was requested on each patient.

Data sought for each patient

1983 questionnaire:
- Family name and initials
- Sex
- Date of birth
- Date of death (if relevant)
- Town of residence
- Name of consultant and hospital giving main clinical care
- Name of consultant and hospital giving shared care (if any)

For those who died:
- Certified cause of death

For new patients after the 1983 return:
- Date of diagnosis
- Mode of death (if relevant):
  - Respiratory failure
  - Hepatic failure
  - Meconium ileus
  - Other, to be specified

The death certification authorities in England and Wales, Scotland, and Northern Ireland were requested to report all deaths with "cystic fibrosis" or any of its synonyms noted anywhere on the death certificate for deaths from 1 January 1977 onwards. For those patients who were reported as dead by clinics but were not initially reported by death certification authorities a request for a search was made to try to reconcile the records. Death certificates of patients who had not previously been reported on were followed up with the certifying physicians.

Great care was taken to identify and eliminate duplicate records. The data are managed using a relational database on a Honeywell computer, and they were analysed by the department of medical computing and statistics, University of Wales College of Medicine.

ANALYSIS

Data collected in this way present some complex analytical problems that have received little attention in other publications on the survival of patients with cystic fibrosis. A study of this sort should ideally yield accurate incidence, prevalence, mortality, and survival figures over a sufficiently long period of time to detect any temporal changes. Experience indicates that circulating questionnaires to clinicians does not lead to complete reporting (some patients reached this database only through death certification). The data are, however, population based and therefore not subject to the many biases of reports from specialist centres where the pattern of referrals is selective. This point deserves considerable emphasis because if extrapolations are to be made from a study of this type it must be clear what selection biases apply. Without a population based study a specialist centre cannot fully elucidate the biases that apply to its sample of the population.

Despite the superiority of the population based approach used in this study there are reasons for possible underreporting. Firstly, infants who die shortly after birth may have had the wrong diagnosis. Secondly, if they were cared for only by a general surgeon they may not have been reported to the survey.

Members of working party: Professor J A Dodge (convenor), Dr Janet Goodall, Dr D Geddes (British Thoracic Society), Dr J M Littlewood, Dr Margaret Mearns, Dr J R Owen, Dr G Russell

Correspondence to: Professor J A Dodge, Institute of Clinical Science, Queen's University, Grosvenor Road, Belfast BT12 6BJ.

Thirdly, in a substantial proportion of patients with cystic fibrosis it is not diagnosed, and hence not reported, until they are several years old. Finally, some patients with less severe features of the disease may receive care from someone who was not a respondent to the survey.

As most of the respondents were paediatricians, data for patients beyond the age of 15 are likely to be incomplete and should therefore be treated with circumspection.

To ascertain true incidence rates—that is, the birth of all children with cystic fibrosis by comparison with all births in the UK—would require that every case was diagnosed and reported by the time of analysis. The effect of underreporting from the questionnaires on the calculation of incidence for earlier years will eventually be minimised by data from death certificates being extrapolated back to the time of birth.

To obtain true prevalence data for a point in time requires complete recording of all cases in the UK at that time. Because of delay in diagnosis true prevalence will inevitably be underestimated in the younger age groups. We therefore extrapolated from the age group structure for earlier years to obtain an estimate for the total prevalence for the UK for mid-1985. In the older age groups the restricted range of the respondents similarly leads to an underestimate of prevalence, as the death certification data showed.

Calculations of mortality present problems with regard to underascertainment. As the calculation of the mortality for any time period requires both a numerator (number of deaths in that period) and a denominator (number at risk of dying at the middle of that period) the rate could be reduced by an underestimate of the numerator or inflated by an underestimate of the denominator. When a patient becomes known to the survey only after death he or she contributes to the denominator in each year from birth to death and to the numerator in the year of death. Each live patient not yet reported—perhaps not yet diagnosed—is missing from the denominator and hence the appropriate figures for mortality are marginally inflated.

These considerations and a pragmatic interpretation of the apparent completeness of the data led us to exclude all patients from analysis who were not alive at some time during the period from 1 January 1977 to the current "cut off date" of 30 September 1985. Figures for mortality rather than for survival are used to compare subgroups of the population to avoid the cumulative effect of selection biases that might occur in survival figures. It is also suggested that mortality should be used for all comparisons between clinics and between countries.

The important question of whether care for patients with cystic fibrosis in specialist clinics leads to better survival is complex and will be reported on later. We present here a comparison between "large" and "small" clinics as an initial and very rough proxy. The definition used for this classification was independent of a knowledge of outcome and was based on an inspection of the frequency distribution of numbers of patients registered with the clinics and alive on 30 June 1985. This distribution showed a gap at about 40 patients that cut the population roughly in half, so this was used as the dividing line. For comparisons between large and small clinics a limited subset of cases had to be used. Patients reported on by more than one hospital were excluded, some being known to as many as four different clinics. There was often no note on the return form that these patients were receiving shared care, so it was impossible to decide whether they had been transferred, were attending two clinics or more in a shared care arrangement (and if so what the extent of the sharing was), or had merely obtained more than one opinion but were being managed in one unit only. They clearly did not conform to a uniform identifiable pattern of care. Also excluded were those who were ascertained initially through death certification. This last group inevitably has a 100% mortality so that the subset on which interclinic comparisons were performed shows substantially higher mortality than the total group.

Life table survivorship was calculated both by the usual "current life table" method[5] for the full age range with an allowance for varying duration of observation and by the "cohort life table" method for the limited age range for which a full cohort of patients has been observed.[6] The current life table calculation is the method used to estimate long term survival when data are available for a limited time only. The method assumes that the current calculated age specific probability of death will apply to the cohort born in the current year for each appropriate year of their life. This method yields a good estimate of the present situation when the age specific death rates are stable through time. Age standardised mortality was calculated by the direct method using the age distribution of survivors in the whole survey as a standard.

Results

The initial questionnaire was sent to 553 paediatricians and 512 adult chest physicians. There was a 99% response rate from paediatricians, with 338 reporting on patients with cystic fibrosis. As relatively few adult chest physicians treat patients with cystic fibrosis, it was not surprising that only 184 (36%) responded, 87 of whom reported on patients with cystic fibrosis. Reports were also obtained from doctors and patients who had seen the notices in the press.

After the follow up survey, in which about 1000 members of the British Thoracic Society were also contacted, a total of 396 paediatricians (including 10 paediatric surgeons) and 191 adult chest physicians reported on patients to the study. At the time of analysis a total of 6220 patients were in the database who had been alive at some point during 1 January 1977-30 September 1985.

Death certificates (for deaths within the above dates) were received for a total of 1378 patients, 80 of whom had not previously been known to the survey. Thirty one deaths reported by physicians had not been confirmed by the death certification authority at the time of the analysis.

Incidence—As the data on births from 1977 and 1978 are the most complete because of both better ascertainment and extrapolation back from death certification they were used to obtain the best estimate of national incidence, which is one case in 2500 births.

Prevalence—Table I gives the derived mid-year prevalence in different age groups for the different years of the study. The 1985 prevalence is also given with an adjustment to take into account the probable

TABLE I—*Mid-year total prevalence of cystic fibrosis in the UK*

Year	Age (years) 0-<1	1-4	5-14	15-24	25+	Total
1977	219	1027	2092	574	91	4003
1978	240	978	2146	647	102	4113
1979	279	969	2143	734	113	4238
1980	266	953	2153	826	128	4326
1981	253	969	2162	912	143	4439
1982	278	1013	2134	998	160	4583
1983	244	1047	2124	1090	192	4697
1984*	198	1015	2158	1147	218	4736
1985*	201	940	2186	1221	246	4794
	(276)	(1047)	(2186)	(1221)	(246)	(4976)

*It is likely that there is poor ascertainment in the 0-<1 and 1-4 year old groups owing to delayed diagnosis. Making an allowance for this produces the estimated numbers in parentheses.

underascertainment of patients aged under 5 years caused by delays of diagnosis and reporting. This adjusted prevalence should be closer to the true state than that calculated from the raw data.

Patterns of Care in 1985—Overall, 276 (5·7%) patients travelled to a hospital outside their region of residence (counting the four Thames regions as one) for their main specialist care; 2454 (51%) patients attended the 28 centres which had 40 or more patients with cystic fibrosis. Further regional analysis of incidence, prevalence, and survival showed no important differences.

Deaths—The distribution of the ages at death of these patients shows that 163 out of the total of 1405 deaths occurred in the first year of life. Of the deaths in the first year, 62 (38%) occurred in the first month and 35 (21%) in the first week of life. Meconium ileus was recorded on the death certificate for just under half of those for whom the reason for death is known in the first year of life and for nearly all deaths within the first month. In the mid-1970s more than 10 deaths a year were being reported with meconium ileus as the cause, giving a first year mortality of 4% from this alone. For 1984-5 combined three deaths only were reported with meconium ileus as the primary cause. This high mortality rate in the first few weeks of life shows the importance of having a population base for comparison of survival. If a specialist centre receives a proportion of its patients by referral only after those who die in the first month of life are excluded its overall survival rates will appear to be considerably better.

Age and sex differences in mortality—Table II shows the mortality by age and sex for all patients observed during the period 1 January 1977-30 September 1985.

TABLE II—*Age specific annual mortality per 1000 population; 1977-85 (Numbers of deaths in parentheses)*

Age (years)	Males (n=3305)	Females (n=2914)	Total
0	70·6 (83)	82·0 (84)	75·9
1-4	11·9 (54)	17·2 (71)	14·5
5-9	20·5 (110)	29·9 (144)	25·0
10-14	33·3 (152)	43·9 (175)	38·3
15-19	41·7 (123)	62·8 (153)	51·2
20-24	70·4 (103)	66·3 (66)	70·6
25-29	84·9 (35)	40·7 (17)	67·0
30-34	81·6 (12)	82·0 (10)	81·0

The high rate in the first year of life drops sharply and then progressively rises to the 20-24 year quinquennium. Although figures are given beyond this age group, they may not present a true picture because of the limitations of the data. The sex difference in mortality, however, shows up clearly with the age specific mortality for females exceeding that for males in all the age groups for which the data are reasonably reliable. Beyond age 20 there seems to be a reversal of this trend, but the numbers are insufficient to be sure of a real effect.

Temporal changes in survival—The age specific mortality was computed separately for deaths in the period 1977 to 1979 and the period 1980 to 1985 (table III). There is a clear trend of improved survival in the more recent time period in all groups except for boys aged 10 to 14.

TABLE III—*Age specific annual mortality per 1000 population and deaths by time and sex (Numbers of deaths in parentheses)*

	Males			Females		
Age (years)	1977-9 (a) (n=2519)	1980-5 (b) (n=3059)	b/a %	1977-9 (c) (n=2271)	1980-5 (d) (n=2648)	d/c %
0	95·9 (38)	57·9 (45)	60	106·3 (40)	66·7 (43)	63
1-4	16·7 (25)	9·6 (29)	57	24·1 (35)	13·5 (36)	56
5-9	23·0 (45)	19·1 (65)	83	34·8 (59)	27·4 (85)	79
10-14	31·2 (45)	34·2 (107)	110	53·4 (69)	39·4 (106)	74
15-19	60·8 (46)	35·4 (77)	58	76·8 (44)	59·8 (109)	78

Differences in mortality by clinic size—Whether the mortality experience is different between large (≥40 patients) and small clinics is inevitably clouded by the patients receiving shared care between a regional cystic fibrosis centre and their local hospital, patients recorded as attending two large or small clinics, and patients known only to the study through death certification and not related to a particular clinic. For those 4940 (79%) attending a single clinic, however, table IV gives age specific mortality and age standardised mortality. Although this subset is not representative of the whole group, the analysis provides some evidence in favour of better survival among patients treated in large clinics.

TABLE IV—*Age specific mortality per 1000 population and deaths by size of clinic for the limited subset of patients recorded as attending a single defined clinic, 1977-85 (Numbers of deaths in parentheses)*

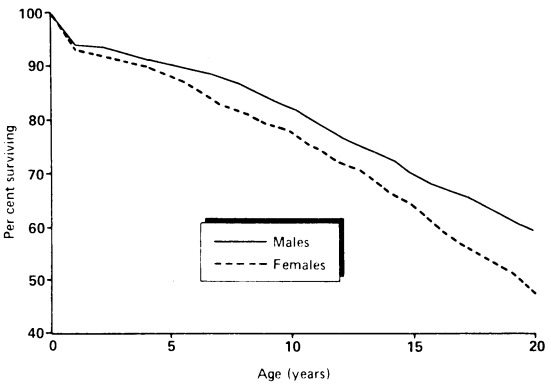
Age (years)	Large clinics* (n=2134)	Small clinics (n=2806)
0	40·3 (34)	42·9 (43)
1-4	6·9 (23)	12·6 (51)
5-9	17·4 (72)	19·0 (85)
10-14	30·5 (96)	36·4 (133)
15-19	50·1 (69)	46·2 (112)
Age standardised	24·8	27·6

*Clinics that treated 40 or more patients at 30 June 1985.

Survival—The use of life tables as a method of expressing survival is based on similar mortality calculations accumulated year by year. To provide a reasonably up to date statement of the survival pattern of the patients in this study the current life table for the two sexes shown in the figure was computed from the mortality experience from 1980 onwards (as in columns (b) and (d) in table III). If mortality has continued to improve this will be an unduly pessimistic description of the survival that patients can now expect. Table V shows the proportion of patients surviving to specified ages.

TABLE V—*Current survival total cystic fibrosis population, 1977-85*

Age (years)	Males	Females	Total
Population survival to specified age (%)			
1	93·2	92·1	92·7
5	88·7	86·5	87·7
10	80·2	74·4	77·4
15	67·7	59·5	63·7
20	55·5	43·4	49·5
25	38·5	31·3	34·9
30	26·3	24·6	25·4
Age at which the population has decreased to the specified proportion			
80% survival	10 years	7 years	8 years
50% survival	21 years	17 years	19 years



The survival of patients with cystic fibrosis from 1 January 1980 to 30 September 1985, for both sexes, based on 3059 males and 2648 females. Calculated on an annual basis using survivorship method[6]

Discussion

The incidence of cystic fibrosis in the population in the UK is apparently slightly higher than previously reported, although it may still be underestimated as it is possible that further births of children with cystic fibrosis will be reported for the years 1977 and 1978, which have been used to calculate our best estimate of incidence. The prevalence data combined with information on the birth rate and incidence of cystic fibrosis give an estimated total prevalence of cystic fibrosis in the UK of 4976 for mid-year 1985. This is, however, likely to be an underestimate because of underascertainment of the number of adults with cystic fibrosis.

The average number of deaths in cystic fibrosis patients per year is roughly 100 less than the number of births as a result of the temporal change in survival, which is shown in table III. The trend is thus for the prevalence to increase by about 100 a year, almost entirely in patients over 15 years of age. The evidence suggests that the numbers of adult patients with cystic fibrosis will continue to increase at a similar though slightly lower rate for another decade at least. The stable prevalence for adults is difficult to estimate because of the limitations of our methods of ascertainment and because there is no evidence that the age specific mortality has stopped improving.

The current survival figures for the years 1977 to 1985 are comparable to those in other reports.[2-4] The difference in mortality between males and females remains pronounced, although the data suggest that survival among females has improved faster than that for males and may even be better after age 20.

The comparison of large and small clinics should be interpreted with considerable caution. The definition of "large" centres in this report is arbitrary and based only on numbers of patients and so does not equate with "specialist" centres. The "large" centres differ widely in type of organisation, number and type of personnel, frequency of follow-up, and clinical management and may not even exist as distinct entities. There is, however, a better survival rate for patients who attend large clinics, although this advantage is not apparent for all ages. The matter of effectiveness and quality of care provided by specialist centres will be discussed in a separate report.

In the mid-1970s meconium ileus accounted for a high mortality in the first year of life. The increased awareness of cystic fibrosis, the improvement in paediatric surgery and neonatal intensive care services, and the close collaboration between surgeons and specialist cystic fibrosis paediatricians have effectively reduced neonatal deaths due directly to meconium ileus. On the other hand, meconium ileus is mentioned as a subsidiary factor on the death certificates of a disproportionately high number of the babies who died in the first year of life, suggesting that there is room for improvement in the aftercare of these patients. There are no data from this survey to show whether the long term outlook for meconium ileus compared with other features of cystic fibrosis is better or worse after the first year of life.

Caring for patients with cystic fibrosis is expensive.[7,8] From these results cautious calculations may be made at the national level of the probable requirements for caring for patients with cystic fibrosis of all ages. It is evident that the number of adults with cystic fibrosis will continue to increase—regardless of impending or future developments in the detection of carriers, prenatal diagnosis, and genetic control. It will also increase regardless of improved paediatric management and either prevention or more effective treatment of respiratory infection.

Data management and statistical analysis were carried out by Dr E C Coles and Dr P A Lewis, department of medical computing and statistics, University of Wales College of Medicine. Research assistants: Mrs C G Turner and Mrs Susan Morison.

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Update box for *Oxford Handbook of Clinical Specialties*, p 597

The new graduated support hosiery

In the United Kingdom elastic stockings are now not prescribed according to type of yarn but by *performance*. This falls into one of three classes.[1] The aim has been to make NHS hosiery more effective, easier to put on, and more acceptable (with fashionable colours and styles).

Class I (old name: lightweight, elastic yarn) Compression at ankle 14-17 mm Hg; at mid-calf <80% of value at ankle; at thigh <85% of value at calf—that is, the compression is *graduated*. Used in venous insufficiency, the aim is to compress the superficial venous system—so forcing blood back into the deep system.
Indications: Early varicose veins; varicose veins in pregnancy.
Styles: Thigh length, below knee, toe open—so foot length matters less—or closed. Open heels are not available.
Colour examples: Tan (Duomed; thigh, below knee, toe closed); mink, honey, or black (Lastosheer Class I Stocking; thigh, below knee, toe closed); dawn (Lastofine; thigh, toe open).

Class II Ankle 18-24 mm Hg; calf <70% of ankle; thigh <70% of calf.
Indications: Varicose veins of medium severity; leg ulcers; mild oedema; varicose veins in pregnancy.
Styles: Thigh length, below knee, toe open or closed.
Colour examples: Mink, honey, or black (Lastosheer Class II Stocking; thigh, knee, toe closed); beige (Lastoyarn Men's Thigh; thigh, below knee, toe open); flesh, peach, grey (Supreme Comfort No 414; thigh, toe closed).

Class III Ankle 25-35 mm Hg; calf <70% of ankle; thigh <70% of calf.
Indications: Gross varicose veins; post-thrombotic venous insufficiency; gross oedema; leg ulcers.
Styles: Thigh length; below knee with knitted heel; toe open or closed. Heels may be open or closed.
Colours: Tan (Duomed; toe open, heel closed); light (Eesilite; toe closed, heel closed); neutral (Lastothread; toe open, heel open). All these may be either thigh or knee length.

Measurement Measure the thinnest part of the ankle, the fattest part of the calf, and the mid-thigh circumference (cm); 80% of patients will conform to a stock size. Examples below are of Duomed.

	Small	*Medium*	*Large*	*Extra large*
Ankle	19-21	22-24	25-27	28-30
Calf	28-34	32-38	36-42	40-46
Thigh	42-56	48-62	54-68	60-74

Made to measure stockings are available in all three classes (and are the only way to obtain class I or II stockings with *open* heels[2]).

Prescribing The doctor specifies the length and number of garments (not pairs) and the class. Other variables may be left to the patient's choice. The pharmacist may do the measuring.

Problems Putting on stockings can be difficult. Wearing rubber gloves helps the process, as does putting on a nylon stocking first.
Twice weekly washing (in warm water, not hot) prolongs the life of stockings—but avoid wringing them out.
Limb ischaemia is a contraindication to the use of support hosiery.—J M LONGMORE

Principal sources

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