Clinical outcomes of Queensland children with cystic fibrosis: a comparison between tertiary centre and outreach services

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ABSTRACT

Objective: To evaluate and compare the clinical outcomes of children with cystic fibrosis (CF) managed primarily at a tertiary cystic fibrosis centre (CFC) with those treated at regional centres by local health care professionals and the cystic fibrosis outreach service (CFOS).

Design, setting and patients: Retrospective study of 273 children with CF born between 19 October 1982 and 19 February 2002 and with clinical data available between 1 January 2000 and 31 December 2002. Patients were grouped into CFC ($n = 131$) or CFOS ($n = 142$), with CFOS then further categorised into three groups depending on the level of care they received.

Main outcome measures: Pulmonary function, *Pseudomonas aeruginosa* status, height and weight *z* scores, and hospital admission rates.

Results: There were no significant differences in pulmonary function, *P. aeruginosa* status, or height and weight *z* scores between children managed by CFC or by CFOS. Children receiving more care at the CFC (level of care [LOC] 1 and 2) were more likely to have multiple hospital admissions than children receiving more care in regional areas (LOC 3 and 4) ($P < 0.001$).

Conclusion: The CFOS model provides effective delivery of specialised multidisciplinary care to children and adolescents living in rural and regional Queensland.

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In 2001, there were 2311 people in Australia with cystic fibrosis (CF); two-thirds of these were children and adolescents.[1] Long-term survival for children with CF has improved markedly, with a predicted mean life expectancy of about 40 years.[2] The reasons for improved survival include earlier diagnosis with neonatal screening, improved nutrition and management of respiratory infections, and management in a tertiary cystic fibrosis centre (CFC).[3-6] It is recommended that children with CF have at least quarterly visits to a multidisciplinary team at a CFC.[4,7-9]

People living in rural and remote Australia have poorer health than those living in metropolitan zones, with higher mortality and lower life expectancy.[10] Specialist outreach clinics have evolved across almost all clinical disciplines in many different countries as a means of providing specialist care for patients in remote areas. The CF clinic at the Royal Children's Hospital, Brisbane, provides cystic fibrosis outreach services (CFOS) at seven sites in Queensland: Cairns, Townsville, Mackay, Rockhampton, Hervey Bay, Toowoomba, and the Gold Coast, with the greatest distance being 1700 km from the tertiary centre. The teams attending CFOS usually include a respiratory physician, physiotherapist, dietitian and nurse. Local health workers are invited to attend the clinics. Children attending outreach clinics are also managed by their local paediatrician or general practitioner. Outreach clinics occur twice a year, except at one site, which has one clinic and two telehealth clinics per year. Some form of CF education or post-clinic multidisciplinary meeting has been provided for local health care teams at least once a year at most sites.

Most studies comparing patients treated at CFCs with those treated in non-CFC settings have found better outcomes in CFC-treated patients.[3,8,11] Our hypothesis was that children attending the CFOS would have worse clinical outcomes than children attending the CFC, and our aim was to determine the differences in clinical outcomes between children with CF treated primarily at a CFC and those treated at regional centres by local health care professionals and the CFOS.

METHODS

Children included in the study were born between 19 October 1982 and 19 February 2002, had a proven diagnosis of CF (either positive sweat testing or the carriage of two CF gene mutations), and had clinical data available between 1 January 2000 and 31 December 2002. Available data on patients who died (6), transferred to adult care (11), or were lost to follow-up (2) during this period were included.

Patients were divided according to the level of care (LOC) they received (Box 1). The criteria for determining the LOC categories were drawn from the *Clinical practice guidelines for cystic fibrosis*,[7] and reflected frequency of review by the CFOS and whether the CFOS was multidisciplinary. The degree of remoteness was calculated for all patients using the Accessibility/Remoteness Index of Australia (ARIA).[12]

Patients were categorised into four groups by birth cohort: 0–4 years old, 5–9 years old, males aged 10 years and older, and females aged 10 years and older. Genotypes were grouped as homozygous delta F508 mutation (ΔF508/ΔF508), heterozygous delta F508 mutation (ΔF508/other), no delta F508 mutation (other/other), or not available.

The study was approved by the Royal Children's Hospital and Health Service District Ethics Committee.

Clinical outcomes

Pulmonary function tests

Pulmonary function data were collected from database records for patients aged 8 years and older. Forced expiratory volume in 1 second (FEV_1) was measured at CFCs (Vitalograph Compact II, Fisher & Paykel, Melbourne, VIC) and at CFOS (Microlab 3300, Micro Medical Ltd, Rochester, UK) according to American Thoracic Society guidelines.[13] The best of three maximal forced expiratory manoeuvres was recorded, and expressed as a percentage of predicted normal reference values based on the patient's height, age and sex.[14] Pulmonary function rate of change from 1 January 2000 to 31 December 2002 was calculated by simple linear regression using two methods: using all FEV_1 % predicted measurements available for each child against time (slope FEV_1 %), and using only the first and last FEV_1 % predicted measurements available for each child against time (first to last FEV_1 %).

Lung function severity was categorised according to the maximum FEV_1 % pre-

dicted as normal lung function (≥ 90% predicted FEV_1), mild impairment (70%–89% predicted FEV_1), moderate impairment (40%–69% predicted FEV_1) and severe impairment (< 40% predicted FEV_1).

Sputum bacteriology

Sputum samples were collected where possible. For children who were unable to expectorate sputum, samples were collected from oropharyngeal specimens or bronchoalveolar lavage. Standard routine microbiological techniques are used at all laboratories. Patients were considered never, intermittently or chronically infected with *Pseudomonas aeruginosa* according to published guidelines.[9]

Nutritional status

Anthropometric variables were obtained with each clinic visit, and heights and weights were expressed as *z* scores.[15] To allow for comparisons with the Australasian CF Data Registry 2001,[1] mean height and weight *z* scores were distributed from < –3 to > 3.

Hospital admissions

We obtained numbers of hospital admissions where CF was the reason for admission during the 3 years from 1 January 2000 to 31 December 2002 from all Queensland hospitals.

Statistical analysis

Analysis was performed using SPSS, version 13 (SPSS Inc, Chicago, Ill, USA). Associations between categorical variables were tested using the χ^2 test of association. $P < 0.05$ was regarded as significant. Differences in patients' characteristics were assessed by one-way analysis of variance for pulmonary function and anthropometric measurements. Potential confounding was checked using general linear models and adjustment was made where necessary for comparisons between LOC categories.

RESULTS

There were 273 patients with CF aged between 0 and 20 years, with median age 9 years (interquartile range [IQR], 5–13 years), including 131 (48%) from the CFC. Over the 3-year period of data collection, no patient changed LOC category. Patient characteristics for age, sex and genotype were similar across the LOC domains (Box 2) and the ARIA domains. Six patients (2.2%) died during the 3-year period (two from LOC 1, three from LOC 2, and one from LOC 4).

1 Level of care categories

Level of care	Description
Cystic fibrosis centre (CFC)	
LOC 1	• All care is provided by the CFC • Admissions to the CFC when required • Outpatient review at CFC three or more times per year
Cystic fibrosis outreach service (CFOS)	
LOC 2	• Children living in regional centres and attending CFOS who also attend CFC regularly • Admissions to CFC or local hospital with local hospital care provided by local paediatrician • Outpatient review by CFC or CFOS three or more times per year
LOC 3	• Care is predominantly provided by the local paediatrician with consultation with CFC • Admissions to local hospital with care provided by local paediatrician • Outpatient review by CFOS at least twice a year
LOC 4	• Involvement by CFC or CFOS once a year or no CFC/CFOS involvement • Includes children seen by respiratory physicians but with no CFC or CFOS multidisciplinary health care involvement • Alternatively, care provided by local paediatrician or general practitioner or unknown ◆

Clinical outcomes

Pulmonary function

Pulmonary function data were available for 150 patients (55%). There were no significant differences between the LOC groups for availability of pulmonary function data ($P = 0.79$), or for maximum FEV_1 % predicted as categories ($P = 0.84$) or mean values ($P = 0.94$) (Box 2 and Box 3). Intermittent or chronic *P. aeruginosa* infection was associated with worse pulmonary function ($P = 0.041$) (Box 3). There were no significant differences between LOC groups for rate of change of pulmonary function as measured by slope ($P = 0.24$) or first to last ($P = 0.09$). Similarly, there was no significant association between *P. aeruginosa* status and rate of change of pulmonary function (slope: $P = 0.95$; first, last: $P = 0.79$).

Comparing maximum FEV_1 % predicted with published data from the Australasian CF Data Registry 2001 ($n = 1101$), our cohort ($n = 150$) had significantly better lung function. Seventy-five children and adolescents (50%) had normal lung function compared with 397 children and adolescents (36.1%) from the Australasian CF Data Registry 2001, and fewer children and adolescents had mild (51; 34%), moderate, (20; 13%) or severe (4; 3%) lung function impairment compared with 443 (40.2%), 227 (20.6%) and 35 (3.2%), respectively, for children and adolescents from the Australasian CF Data Registry 2001 ($P = 0.008$). Children with multiple admissions were more likely to have more severe lung disease, and this was independent of LOC ($P < 0.001$).

P. aeruginosa status

Sputum analysis was available for 243 (89%) of the 273 patients. There was no difference in sputum culture availability between the LOC categories ($P = 0.47$) (Box 2). *P. aeruginosa* status was not significantly different across LOC groups ($P = 0.39$). The proportion of children with chronic *P. aeruginosa* infection increased with age ($P < 0.01$) from 16% for 0–4-year-olds, to 32% for 5–9-year-olds and 81% for children aged 10 years and older.

Nutritional status

There were no significant differences in mean height *z* scores ($P = 0.65$) or mean weight *z* scores ($P = 0.56$) by LOC (Box 4). The *z* scores for height and weight declined with increasing age, but this was only significant for weight ($P = 0.01$). Mean *z* scores for height (–0.47; 95% CI, –0.59 to –0.36) and weight (–0.34; 95% CI, –0.46 to –0.23) were significantly lower than the normal population mean *z* score of 0 ($P < 0.01$). The distribution of height and weight *z* scores

was similar to child and adolescent height and weight *z* scores published in the Australasian CF Data Registry 2001 ($P = 0.63$).[1]

Mean weight *z* scores were significantly affected by *P. aeruginosa* infection ($P = 0.003$) (Box 4). To correct for the effect of age, the mean weight *z* scores were stratified for age and sex. The relationship between *P. aeruginosa* infection and weight was mostly explained by the 0–4-year-old group, where those with *P. aeruginosa* infection had a significantly lower ($P = 0.026$) weight *z* score (–0.58; 95% CI, –1.04 to –0.13) for intermittent infection and (–0.63; 95% CI, –1.35 to 0.09) for chronic infection, compared with (0.09; 95% CI, –0.26 to 0.43) for children not infected with *P. aeruginosa*. For children aged 5 years and older, we found no significant relationship between mean weight *z* scores and *P. aeruginosa* status.

Admission rates for CF-related illnesses

Children in LOC 1 and LOC 2 were more likely to have multiple admissions than children in LOC 3 and LOC 4 ($P < 0.001$) (Box 2). For LOC 2, 49% of admissions were to the CFC. Children aged 5–9 years were less likely to be admitted (38%) than children aged 10 years and older (62%), who were more likely to have multiple admissions ($P = 0.04$). Multiple admissions were more likely with chronic *P. aeruginosa* infection (89/141; 63%), compared with no (27/141; 19%) or intermittent (25/141; 18%) *P. aeruginosa* infection ($P < 0.01$).

2 Clinical characteristics and demographics of children attending a cystic fibrosis centre and/or a cystic fibrosis outreach service

	CFC		CFOS			
	LOC 1	LOC 2	LOC 3	LOC 4	Total	*P*
Number	131	35	72	35	273	
ARIA category						
Highly accessible	113 (86%)	14 (40%)	38 (53%)	23 (66%)	188 (69%)	< 0.001
Accessible	10 (8%)	16 (46%)	20 (28%)	5 (14%)	51 (19%)	
Moderately accessible	8 (6%)	2 (6%)	9 (12%)	4 (11%)	23 (8%)	
Remote	0	1 (3%)	2 (3%)	3 (9%)	6 (2%)	
Very remote	0	2 (6%)	3 (4%)	0	5 (2%)	
Sex and age group						
Boys and girls 0–4 years	28 (21%)	9 (26%)	21 (29%)	6 (17%)	64 (23%)	0.59
Boys and girls 5–9 years	38 (29%)	8 (23%)	23 (32%)	7 (20%)	76 (28%)	
Males ⩾ 10 years	35 (27%)	8 (23%)	15 (21%)	13 (38%)	71 (26%)	
Females ⩾ 10 years	30 (23%)	10 (29%)	13 (18%)	9 (26%)	62 (23%)	
FEV_1 % predicted*						
No data	57 (44%)	14 (40%)	35 (49%)	17 (49%)	123 (45%)	0.79
⩾ 90%	40 (54%)	10 (48%)	17 (46%)	8 (44%)	75 (50%)	0.84
70%–89%	23 (31%)	7 (33%)	15 (41%)	6 (33%)	51 (34%)	
40%–69%	8 (11%)	3 (14%)	5 (13%)	4 (22%)	20 (13%)	
< 40%	3 (4%)	1 (5%)	0	0	4 (3%)	
Genotype						
ΔF508/ΔF508	72 (55%)	12 (34%)	33 (46%)	16 (46%)	133 (49%)	0.45
ΔF508/other	48 (37%)	16 (46%)	27 (37%)	12 (34%)	103 (38%)	
Other/other	4 (3%)	2 (6%)	4 (6%)	2 (6%)	12 (4%)	
Not available	7 (5%)	5 (14%)	8 (11%)	5 (14%)	25 (9%)	
Pseudomonas* status						
No data	14 (11%)	3 (9%)	7 (10%)	6 (17%)	30 (11%)	0.47
No infection	35 (30%)	6 (19%)	21 (32%)	5 (17%)	67 (28%)	0.39
Intermittent infection	16 (14%)	8 (25%)	13 (20%)	7 (24%)	44 (18%)	
Chronic infection	66 (56%)	18 (56%)	31 (48%)	17 (59%)	132 (54%)	
Admission rates						
No admissions	28 (21%)	1 (3%)	27 (37%)	17 (49%)	73 (27%)	< 0.001
1 admission	31 (24%)	8 (23%)	12 (17%)	5 (14%)	56 (20%)	
⩾ 2 admissions	72 (55%)	26 (74%)	33 (46%)	13 (37%)	144 (53%)	

ARIA = Accessibility/Remoteness Index of Australia. CFC = cystic fibrosis centre. CFOS = cystic fibrosis outreach service. FEV_1 = forced expiratory volume in 1 second. LOC = level of care.
* Percentages for FEV_1 and *Pseudomonas aeruginosa* status are of the total for whom data were available. ◆

DISCUSSION

To our knowledge, this is the first reported study to compare clinical outcomes between children with CF receiving treatment at a specialist CFC with children having care in regional centres with specialist outreach services. We did not find poorer clinical outcomes in the CFOS-managed patients.

There were a number of weaknesses in our study. Despite relatively large study numbers, limitations apply to analysis of small subgroups. The LOC 4 group had less data available for analysis, particularly for analysis of pulmonary function rate of change, so these data should be interpreted with caution. In addition, patients in LOC 1 had pulmonary function measured at every visit, including when they presented with pulmonary exacerbations, whereas children seen in the regional areas by CFOS would only have pulmonary exacerbations recorded by chance if they coincided with the outreach visit. Only the maximum measurement has been reported here, although all data were included to estimate slope. A high proportion of patients had normal lung function, and this may have limited our ability to detect differences between groups. There can be considerable discrepancy between lung function and structure, and advanced structural damage can be present in lungs of patients with normal lung function.[16] More sensitive methods, such as high-resolution computed tomography, may be better at detecting differences between patient groups in which there is a high percentage of normal pulmonary function. The levels of service provision in different regional centres were also quite heterogeneous, with some centres having fewer resources. This may explain why some patients in LOC 2 were seen at both the CFC and the CFOS although, as the admission rates were highest in LOC 2, it may have

3 Pulmonary function data

	FEV_1 % predicted (maximum)				Slope FEV_1 % per year				First to last FEV_1 % per year		
	n	Mean	95% CI	*P*	*n*	Mean	95% CI	*P*	Mean	95% CI	*P*
Level of care											
LOC 1	74	86.9	82.1 to 91.7	0.94	67	−1.5	−2.9 to −0.1	0.24	−1.4	−2.9 to 0.1	0.09
LOC 2	21	84.9	75.0 to 94.8		19	−1.4	−5.0 to 2.2		0.5	−4.0 to 5.0	
LOC 3	37	86.0	80.7 to 91.2		30	0.7	−2.3 to 3.6		1.0	−2.1 to 4.1	
LOC 4	18	84.2	75.9 to 92.4		11	1.8	−1.0 to 4.7		4.3	−1.5 to 10.1	
***Pseudomonas* status**											
No infection	20	96.2	90.2 to 102.1	0.041	13	−0.4	−4.2 to 3.4	0.95	−0.3	−4.5 to 4.0	0.79
Intermittent infection	17	84.7	76.5 to 92.9		13	−0.3	−4.5 to 4.0		1.4	−4.7 to 7.5	
Chronic infection	108	84.3	80.4 to 88.2		97	−0.8	−2.1 to 0.6		−0.1	−1.6 to 1.3	

FEV_1 = forced expiratory volume in 1 second. LOC = level of care. ◆

been due to patients in this group being sicker despite having no difference in other clinical outcomes.

Patients seen at the CFOS were reviewed twice a year by the CF specialist team whereas patients attending the CFC were likely to be seen more frequently. Although the clinical outcomes were similar in both groups, the study was not designed to examine frequency of review by a CF specialist team. In addition, the quality of review, involvement of local teams, and the educational component may be important determinants of outcome.

Variability in sputum analysis between laboratories prevented differentiation between mucoid and non-mucoid strains of *P. aeruginosa*, which has also been reported in another study,[17] and microbial sensitivity patterns could not be examined because of variability of testing methods between laboratories.

Children receiving CFOS care had the same prevalence of intermittent and chronic *P. aeruginosa* infection as those attending the CFC. Our study also supports the existing evidence that *P. aeruginosa* infection increases with age[17] and is associated with poorer pulmonary function[18-21] and higher rates of admissions.[18]

A significant association was found between early infection with *P. aeruginosa* and reduced weight in the 0–4 years age group. This is in contrast to another study that found no significant difference in weight or height, which was attributed to aggressive therapeutic and nutritional interventions.[22] However, unlike in our study, patients were not diagnosed through neonatal screening, with most diagnoses due to poor growth, and symptoms of malabsorption. This suggests that the subjects in the earlier study were already likely to be undernourished, perhaps making it more difficult to detect the effect of early *P. aeruginosa* acquisition.

Studies, including a Cochrane review of 73 studies, of specialist outreach clinics in primary care and rural hospital settings in 14 countries across five continents have shown that simple consultation-based outreach services improve patient access but have no effect on health care outcomes. However, more complex multifaceted outreach clinics that involve collaboration with primary care, education and other services are associated with improved health care outcomes and more efficient and guideline-consistent care.[23,24] There is an active education program by the CFOS, and an annual CF education course has been available in Brisbane for health care professionals, which may have contributed to the good outcomes in patients managed in outreach in this study.

In conclusion, our study demonstrates adequate clinical outcomes in rural CF patients receiving an outreach model of care, when compared with the CFC-treated population. Additional support of the CFOS model of care comes from a recent report of equivalent health-related quality of life in children with CF living in regional Queensland compared with those attending the CFC.[25] Differences between CFC and CFOS care may not be apparent until more sensitive outcome measures are used or until longitudinal observational studies over a

4 Height and weight *z* scores

		Height			Weight		
	n	Mean	95% CI	*P*	Mean	95% CI	*P*
Level of care							
LOC 1	131	−0.50	−0.64 to −0.35	0.65	−0.38	−0.54 to −0.23	0.56
LOC 2	35	−0.35	−0.68 to −0.03		−0.17	−0.50 to 0.16	
LOC 3	72	−0.55	−0.78 to −0.32		−0.40	−0.62 to −0.17	
LOC 4	30	−0.35	−0.77 to 0.08		−0.23	−0.62 to 0.15	
Sex and age group							
Boys and girls 0–4 years	64	−0.39	−0.61 to −0.16	0.13	−0.23	−0.45 to −0.01	0.01
Boys and girls 5–9 years	76	−0.32	−0.54 to −0.11		−0.14	−0.35 to 0.07	
Males ⩾ 10 years	67	−0.66	−0.87 to −0.46		−0.63	−0.84 to −0.42	
Females ⩾ 10 years	61	−0.54	−0.80 to −0.28		−0.41	−0.67 to −0.14	
***Pseudomonas* status**							
No infection	67	−0.30	−0.53 to −0.07	0.07	−0.05	−0.28 to 0.18	0.003
Intermittent infection	44	−0.65	−0.93 to −0.36		−0.43	−0.72 to −0.13	
Chronic infection	127	−0.60	−0.76 to − 0.43		−0.53	−0.68 to −0.37	

LOC = level of care. ◆

longer period (ie, 10 years) are undertaken. Additional research addressing the influence of other services, such as telemedicine, workshops, outpatient intravenous treatments and alternative outcome measures, such as survival rates and patient–carer treatment preferences are required, as well as studies of the cost-effectiveness of the CFOS model of service delivery.

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COMPETING INTERESTS

None identified.

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