Health-related quality of life in Cystic Fibrosis patients infected with transmissible *Pseudomonas aeruginosa* strains: cohort study

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DECLARATIONS

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MJW designed the study and edited the manuscript; AA conducted the study and wrote the draft of the manuscript; MS and JM carried out the statistical analysis and edited the manuscript; MJL edited the manuscript

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Summary

Objectives To assess the impact on health-related quality of life (HRQoL) in adult cystic fibrosis (CF) patients of chronic infection with the Liverpool Epidemic Strain (LES) of *Pseudomonas aeruginosa* (Psa).

Design Cohort study.

Participants Adult CF patients attending a single CF centre.

Setting Outpatient clinic.

Main outcome measures HRQoL measures of adult CF patients chronically infected with LES and Psa strains measured by CFQ-UK.

Results Patients infected by transmissible Psa strains had worse physical functioning, respiratory symptoms, treatment burden, vitality, role, health perception and emotion than those with unique Psa strains ($P < 0.01$), and significantly poorer physical functioning, respiratory symptoms, treatment burden, body image, weight, role, and emotion than those without any Psa infection ($P < 0.05$). Furthermore, in a matched cohort of 39 patients, those with LES infection reported significantly worse physical functioning, treatment burden, respiratory symptoms and health perception than those with unique Psa infection ($P < 0.02$).

Conclusion Chronic infection with transmissible Psa strains, particularly LES, confers a worse quality of life in adult CF patients. Coupled with the established poorer clinical outcome, this reinforces the need to prevent the spread of such strains in CF community.

Introduction

Cystic fibrosis (CF) is the commonest potentially lethal inherited disease in the Western world. Although it is incurable, survival in CF has improved over the years and current epidemiological data suggest that the average life expectancy of an individual born with CF in the UK is now 38 years.[1] However, this is at the expense of a high treatment burden, particularly in those chronically infected with *Pseudomonas aeruginosa* (Psa) which is known to confer increased morbidity and mortality[2,3] and may therefore diminish their quality of life (QoL).

The World Health Organization (WHO) has defined health as 'a state of complete physical, mental and social well being and not merely the absence of disease or infirmity',[4] and therefore,

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in CF managing the patient's psychological and psycho-social wellbeing, which influence their QoL, is as important as managing the physical aspects of their disease.

Health-related quality of life (HRQoL) questionnaires can describe health outcomes in ways that are meaningful to patients and families as well as to healthcare professionals, and recently a disease-specific HRQoL questionnaire (the CFQ-US) has been developed for patients with CF, and a UK version of this (the CFQ-UK) has been validated for use without the loss of its psychometric properties.[9]

Although several studies have looked at QoL in CF, few have investigated how an individual patient's disease state, particularly infection with Psa, may impact on this. Recently, transmissible Psa strains have been identified, the most important of which is the Liverpool Epidemic Strain (LES)[5] now widespread throughout UK CF centres,[6] has also been reported in Canada[7] and is associated with a worse clinical outcome.[8] We have a high incidence of LES Psa infection in CF patients attending our adult clinic: we were therefore interested to look at the effect of Psa infection, and in particular that due to LES, on the quality of their lives and used the CFQ-UK for this purpose.

Methods

All 204 patients in a clinically stable state (i.e. no exacerbation within the previous 4 weeks) attending a routine outpatient visit between August 2009 and March 2010 formed the potential study population. Those with atypical CF or chronically infected with *Burkholderia cepacia complex* were excluded. Of the remaining 168 patients, 11 (5%) refused to take part. Following informed consent, 157 patients completed the CFQ-UK (Teen/Adult revised, version 1)[9] prior to being seen by a healthcare professional. Clinical details (sputum microbiology, lung function, nutritional state and diabetes mellitus) were retrieved from the case records to aid subsequent data analysis. This study was approved by the regional ethics committee (Study Ref no 09/H1013/52: Oldham, Tameside & Glossop & Salford & Trafford Research Ethics Committees).

Psa infection state

All patients submit microbiological samples at every clinic visit/inpatient stay: chronic infection with Psa is defined by at least three positive sputum samples within a 6-month period.[10] Our unit has pioneered Psa genotyping methodology in CF, and we regularly genotype the Psa isolates from our patients to aid cross-infection control measures within the clinic: those without known LES infection undergo genotyping using PCR every 3 months to identify unique and other transmissible Psa strains,[11] while those infected with LES undergo a genotypic check (using PCR and primers PS21 & F9)[12] on a yearly basis. Using this system, we are aware of the Psa genotypes infecting our CF patients at all times.

Based on this, we divided the surveyed patients into three groups: 93 with LES (all infected prior to transfer from the paediatric sector), 44 with other Psa strains (43 infected prior to transfer from the paediatric sector), and the remaining 20 without Psa infection or with persistently negative cultures (six cases had undergone successful Psa eradication since transfer from the paediatric sector) (Table 1).

Statistical analysis and patient matching

The Kruskal-Wallis test was used to determine differences between the three groups on all 12 CFQ-UK domains, and where significant differences were noted individual comparisons between groups were made using the Mann-Whitney U test.

To overcome this, using all available patient data we developed a multivariate logistic regression model and generated a propensity score for LES group membership[13,14] in order to allow matching with patients infected with other Psa strains. A full non-parsimonious model was developed that included FEV1, BMI, age and gender as independent variables and treatment category as the dependent variable. The goal is to balance recorded patient characteristics between treatment groups by incorporating everything recorded that may relate to either systematic bias or simply bad luck.

The regression model had an appropriate fit (Hosmer–Lemeshow goodness-of-fit $\chi^2 = 12.4$

Table 1
Total study population demographics ($n = 157$)

	Psa strain		
	LES	*Other*	*No Psa infection*
Patients (*n*)	93	44	20
Women (%)	38 (51)	16 (38)	9 (48)
Median age, years (IQR)	26 (26–31)	22 (20–28)	21 (19–29)
Mean FEV1% (SD)	65 (23)	69 (23)	77.8 (26)
Mean BMI (SD)	21.7 (3.5)	22.6 (3.6)	25 (4.8)
Diabetes (%)	46 (49)	13 (29)	2 (10)
Enteral feed	5	1	0
TIVAD (%)	45 (48)	8 (18)	3 (15)

and $P = 0.13$) and acceptable discrimination (c statistic, 0.78) indicating an acceptable ability to differentiate between patients with or without LES. We then used a macro (see http://www2.sas.com/proceedings/sugi29/165-29.pdf) to perform propensity-matching. Before matching, the median propensity scores for patients with and without LES were 0.70 and 0.66, respectively (Wilcoxon signed-rank test $P = 0.036$). After matching, the median propensity scores for patients with and without LES were 0.67 and 0.66, respectively (Wilcoxon signed-rank test $P = 0.81$).

Using this technique we were able to match 39 patients chronically infected with LES with 39 patients infected with other Psa strains. We did not attempt to match LES patients with those without Psa, since Psa infection *per se* is known to confer a worse morbidity and mortality.

A $P < 0.05$ was considered to be significant. All statistical analysis was performed using SAS for Windows Version 8.2.

Results

The demographic details and clinical characteristics of the 157 patients who completed the CFQ–UK questionnaire are given in Table 1. In our initial unmatched cohort although there were no significant differences in age or FEV1 between groups, patients chronically infected with LES had a higher disease burden as evidenced by more with CFRD (Cystic Fibrosis Related Diabetes Mellitus), TIVAD (Totally Indwelling Venous Access Device) implantation and the use of enteral feeding (all $P < 0.005$ compared to other groups). Patients chronically infected with LES had a higher disease burden compared to those with other Psa strains or no Psa infection.

Using the Kruskall-Wallis test, comparison across all three groups of patients produced significant differences in nine of the 12 HRQoL domains. Individual comparisons between groups using the Mann-Whitney U test across these nine domains revealed that patients harbouring LES infection had significantly worse physical functioning, respiratory symptoms, treatment burden, vitality, role, health perception and emotion than those with unique Psa strains, and significantly poorer physical functioning, respiratory symptoms, treatment burden, body image, weight, role and emotion than those without any Psa infection. However patients infected with unique Psa strains only reported a worse perception of body image than those with no Psa infection (Table 2).

Furthermore, in the matched cohort of 39 patients (Table 3), those with LES infection reported significantly worse physical functioning, treatment burden, respiratory symptoms and health perception than those with unique Psa infection (Table 4), and five further domains (role, vitality, body image, and emotional and social functioning) approached statistical significance.

Discussion

Although it is known that age, sex, FEV1, nutritional state, the use of indwelling venous devices, pulmonary exacerbations and the presence of diabetes can adversely affect the QoL in CF patients;[15–17] little work has been done on the effect of chronic infection in this group.

Table 2
Difference in HRQoL* domains between LES infection, other Psa infection and no Psa infection groups: Mann-Whitney U test (median score [IQR]) (*higher scores indicate better outcomes) – Unmatched groups

Microbiology	*Other Psa*	*No Psa*	*P*	*LES*	*No Psa*	*P*	*LES*	*Other Psa*	*P*
Physical function	79 (58–96)	75 (56–94)	NS	58 (33–87)	75 (56–94)	0.03	58 (33–87)	75 (56–94)	0.0003
Role	83 (58–100)	83 (62–100)	NS	75 (50–92)	83 (62–100)	0.04	75 (50–92)	83 (58–100)	0.01
Vitality	58 (50–75)	58 (33–91)	NS	50 (33–66)	58 (33–91)	NS	50 (33–66)	58 (50–75)	0.008
Emotion	80 (66–93)	83 (63–93)	NS	73 (53–86)	83 (63–93)	0.05	73 (53–86)	80 (66–93)	0.02
Body image	78 (55–100)	100 (100–100)	0.008	67 (44–100)	100 (100–100)	0.0009	67 (44–100)	77 (55–100)	NS
Respiratory symptoms	67 (50–83)	77 (67–86)	NS	55 (39–72)	77 (67–86)	0.0002	55 (39–72)	67 (50–83)	0.002
Treatment burden	67 (55–76)	72 (33–83)	NS	55 (44–67)	72 (33–83)	0.01	55 (44–67)	67 (55–76)	0.01
Health perception	67 (55–78)	67 (0–89)	NS	55 (33–67)	67 (0–89)	NS	55 (33–67)	66 (55–78)	0.01
Weight	100 (67–100)	100 (100–100)	NS	100 (33–100)	100 (100–100)	0.01	100 (33–100)	100 (100–100)	NS

Table 3
Univariate demographics in LES infected and other Psa infected – matched group Continuous variables are shown as mean (standard deviation) Categorical variables are shown as a number (percentage)

	Other Psa infection (n = 39)	*LES infection (n = 39)*	*P value*
Women (%)	14 (37)	11 (28)	0.36
Age (years)	28 (8)	28 (9)	0.66
BMI (SD)	22.6 (3.6)	22.3 (3.1)	0.80
FEV1(SD)	71 (22)	69 (21)	0.77
Diabetes (%)	11 (28)	18 (46)	0.15
Enteral feeding	1	2	1.00
TIVAD (%)	12 (31)	21 (53)	0.66

Studies looking at *B cepacia* infection have given variable results. Duff[18] showed that segregation from other patients caused feelings of isolation, anger and of being a microbiological 'leper' but did not use objective QoL assessment tools, and although Gee[15] did not demonstrate any excess effect of *B cepacia* infection compared to other organisms, no details of disease severity were recorded and the patient numbers were small.

As regards Psa infection, while Goldbeck[20] suggested that new infection had an independent negative effect on QoL, the study was small and did not achieve statistical significance. Although previous studies addressing the effect of chronic Psa colonization have failed to show any adverse effects, the study by Britto *et al.*[19] had poorly matched groups, used a generic QoL questionnaire (sf-36) and only one-third of the participants were adults, and the study by Havermans *et al.*[21] in 57 adult CF patients did not use patient matching and no information regarding Psa strain types was provided.

To our knowledge this is the first study evaluating the health-related quality of life in a substantial number of Psa-infected adult CF patients including those chronically infected with the most important such transmissible strain, LES. For the first time, we have shown that infection with LES confers a worse quality of life in CF than infection with other Psa strains and those without any Psa, and this was confirmed in matched groups of patients. This is an important

Table 4
HRQoL outcomes* in LES infected and Other Psa infected Matched Groups: Mann-Whitney U test

QoL dimension	*Other Psa infection (n = 39)*	*LES infection (n = 39)*	*P value*
Physical function	84 (63–100)	72 (33–88)	0.02
Role	84 (67–100)	76 (50–92)	0.06
Vitality	59 (50–75)	51 (33–67)	0.06
Emotional function	81 (67–93)	74 (53–93)	0.07
Social function	79 (61–83)	68 (50–83)	0.07
Body image	89 (56–100)	68 (44–100)	0.09
Eating	100 (89–100)	100 (78–100)	0.16
Treatment burden	68 (56–78)	57 (44–67)	0.02
Health perception	68 (56–89)	57 (33–78)	0.01
Weight	100 (67–100)	100 (33–100)	0.36
Respiratory symptoms	73 (50–83)	62 (44–72)	0.006
Digestion	89 (67–100)	89 (67–100)	0.70

*Higher scores indicate better outcomes
Variables quoted as median (interquartile range)

finding that needs to be heeded by the CF healthcare community.

LES first came to light in 1996 at our local paediatric CF centre,[5] and is now widespread throughout UK CF clinics.[6] It has also been reported at a CF centre in Canada.[7] It is highly transmissible – it can super-infect patients already possessing other Psa strains,[22] can spread to non-CF relatives,[23] and also cross-infect other species.[24] We have a large cohort of such patients, mainly inherited from the paediatric sector and have already shown that these patients have a poorer prognosis[8] and increased treatment burden[25] than other (matched) patients. It is therefore not surprising that these individuals also have a poorer quality of life.

Furthermore, LES-infected patients not only scored more poorly in those domains assessing physical wellbeing (physical function, treatment burden, weight, and respiratory symptoms) but also in those assessing psychological functioning (vitality, emotion, health perception and body image). The impairment of physical domain QoL indicators are expected as LES is known to cause a more rapid decline in lung function, weight, and increase the need for IV antibiotics, triggering the need for extra therapy which in turn results in a higher treatment burden. However, the poorer scores in the psychological domain indicators suggest that LES has a more profound effect on these individuals than that expressed by physical deterioration alone. This combination of poor perceived physical parameters (poor physical function, treatment burden, weight, and respiratory symptoms scores) and higher psychological burden (poor vitality, emotion, health perception and body image scores) in patients with LES may result in an overall worse HRQoL compared to those infected with other Psa strains or without Psa infection.

However, the cohort of LES-infected patients in our study were older and had poorer pulmonary function and had a higher disease burden as evidenced by higher incidence of CFRD, those with TIVAD's and needing enteral feeds than the remainder, suggesting that at least some of these differences in quality of life could be due to this. It was for this reason that we compared matched groups, obtained using a validated statistical propensity scoring system. In this matched group of patients infected with Psa strains, those with LES still demonstrated a significantly worse perception of physical (physical function, treatment burden, respiratory symptoms) and psychological (health perception) wellbeing compared to patients with other Psa strains. Furthermore, although other aspects of psycho-social wellbeing (role, vitality, emotional function, social function and body image) failed to achieve statistical significance, there were strong trends, indicating that these changes are a true reflection of the patients' LES infection status. It was for this reason that we opted not to use alpha correction (e.g. Bonferroni) for group matching since the differences between the matched groups (without correction) were close to the level of significance: this is highly unlikely to be a chance occurrence.

In contrast, patients infected with other Psa strains only had an altered body image compared to patients without Psa infection, suggesting that acquisition of sporadic Psa may not significantly impact on the psychological wellbeing of the individual.

It has already been shown that depression and anxiety are more common in CF[26] and can adversely affect their QoL: anxious patients report more respiratory symptoms, have a poorer perception of their health and treatment burden, and poorer social and emotional functioning,

while those with depression show a poorer body image, eating disturbances and emotional functioning.[27] Although our study was not designed to address the prevalence of anxiety and depression among our patients, it may be that these factors also contribute to the poorer QoL outcomes in patients infected with epidemic strains and this merits further study.

This large cross-sectional QoL study adds further evidence to the poor outcomes associated with chronic infection with transmissible Psa strains in CF: those harbouring LES reported worse scores across most HRQoL domains compared to patients without such infection.

There are limitations to our study: we only looked at one centre with a high prevalence of one transmissible Psa strain (LES) and used a cross-sectional design, and it may be that the results cannot be generalized to other transmissible Psa strains or the CF population at large. Nevertheless, LES is the most prevalent transmissible strain in the UK and has already spread to units elsewhere, so our findings will be of relevance to many CF clinics. Also, this is the largest study of the measurement of QoL in adult CF patients, using a new validated tool, which is increasingly being employed in the holistic assessment of this chronic disease group. Although longitudinal studies with repeated QoL measurements before and after chronic infection with such transmissible epidemic strains are needed to address their true effect on QoL in CF patients, our study does highlight the physical as well as psychosocial limitations faced by patients infected with such epidemic strains.

Prevention of cross-infection with transmissible strains is essential to ensure better physical and psychological outcomes for these patients, and such strategies should be adopted by all CF centres.

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