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Changes in Pediatric Health-Related Quality of Life in Cystic Fibrosis After IV Antibiotic Treatment for Pulmonary Exacerbations

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Abstract

Intravenous (IV) antibiotic therapy for pulmonary exacerbations (PE) has been shown to improve pulmonary functioning for patients with cystic fibrosis (CF); however, little is known about its effects on pediatric health-related quality of life (HRQOL). This prospective study assessed the impact of IV treatment of a PE on generic and CF-specific HRQOL for children and adolescents with CF. Participants included 52 children and adolescents with CF experiencing a PE ($M_{\text{age}} = 13.6$ years; 54% males; $M_{\text{FEV}_{1\%}}$ predicted = 58.8%). HRQOL, pulmonary functioning, and body mass index were assessed before and after IV antibiotic treatment. Results of this prospective, observational study indicated significant improvements on CFQ-R Respiratory ($M_{\text{change score}} = 11.7$; 95% CI = 6.3–17.1; $p < .0001$) and Weight ($M_{\text{change score}} = 15.9$; 95% CI = 7.9–23.8; $p < .0001$) scales. The CF-specific measure was more sensitive to changes in HRQOL than the generic instrument. These data suggest that CF-specific HRQOL improves with treatment for a PE with IV antibiotics. The noted statistically and clinically significant changes in the CFQ-respiratory scale indicate that the measure may be beneficial to pulmonary health care teams.

Keywords

Patient-reported outcomes; Intravenous antibiotics; Disease-specific; Minimal clinically important difference

Cystic fibrosis (CF) is the most common life-shortening, autosomal recessive disorder of Caucasian populations. CF is diagnosed in about 1 in 3,400 live births (Kosorok, Wei, & Farrell, 1996), with approximately 30,000 children and adults with CF currently living in the United States (Cystic Fibrosis Foundation, 2007). CF is a complex, progressive disease that affects major organ systems, requiring adherence to a complex treatment regimen, including airway clearance, bronchodilators, inhaled antibiotics, mucolytics, increasing caloric intake, and pancreatic enzymes, in order to prevent infection and slow the progression of disease. Despite these treatments, lung infections or pulmonary exacerbations (PE) may still occur and are considered “one of the most important clinical events for patients with CF in the course of this disease” (Goss & Burns, 2007). The annual rate of CF pulmonary exacerbations has been negatively associated with declines in pulmonary functioning (e.g., forced expiratory volume in one-second percent predicted; FEV_{1%} predicted) and survival rates (Cystic Fibrosis Foundation, 2004; Liou et al., 2001).

Despite the importance of PEs for patients with CF, there is no agreed upon definition of a PE and no standardized tool to identify them (Goss & Burns, 2007). Pulmonary exacerbations are currently defined in clinical trials by the presence of a variable number of the following symptoms: (1) changes in sputum production, (2) increased cough, (3) fever above 38°C, (4) decreased appetite, and (5) decreased lung function, specifically a drop in FEV_{1%} predicted and (6) decreased exercise tolerance (Ramsey et al., 1999; Rosenfeld, 2005). However, in clinical practice, a PE is diagnosed with a combination of signs and symptoms, laboratory data and clinical evaluation. In fact, the U.S. CF Foundation Registry data regarding pulmonary exacerbations is based on patients having a CF-related pulmonary condition requiring a hospital admission or use of home IV antibiotics.

Approximately 35% of children and adolescents with CF experience at least one acute PE each year (Cystic Fibrosis Foundation, 2004). Exacerbations are commonly treated with oral, aerosol, or IV antibiotics (Dakin, Henry, Field, & Morton, 2001). Antibiotic treatments typically occur in the hospital setting for a 10–14 day period; however, more recently approximately 50% of patients are treated with IV antibiotics at home (Cystic Fibrosis Foundation, 2004). Although the use of IV antibiotics for PEs has been successful in improving lung function (Cerny, Cropp, & Bye, 1984; Clayton et al., 1998), few studies have examined the impact of this treatment on health-related quality of life (HRQOL) using well-validated measures, and no studies to date have utilized a disease-specific HRQOL measure in pediatric populations.

HRQOL has been widely accepted as a multi-dimensional construct that includes several domains, such as physical functioning and symptoms, psychological and emotional states, and social functioning (Schipper, Clinch, & Olweny, 1996). These broad constructs are often measured by generic instruments, such as the Pediatric Quality of Life Inventory (PedsQL™; Varni, Seid, & Kurtin, 2001) and the Child Health Questionnaire (CHQ; Landgraf, Abetz, & Ware, 1996), which are often less sensitive to changes that are important for a particular disease (e.g., respiratory symptoms). In contrast, disease-specific measures, such as the Cystic Fibrosis Questionnaire-Revised (CFQ-R; Modi & Quittner, 2003; Quittner, Buu, Messer, Modi, & Watrous, 2005) and the Cystic Fibrosis Quality of Life (CFQoL; Abbott, Webb, & Dodd, 1997) are better able to assess changes most relevant for this population (e.g., respiratory symptoms, treatment burden, role functioning, and eating problems). In fact, a recent US Food

and Drug Administration (FDA) consensus report on patient-reported outcomes (PROs) has called for the use of well-validated, clinically meaningful HRQOL measures as both primary and secondary endpoints in clinical trials (Goss & Quittner, 2007; U.S. Food and Drug Administration, 2006). Well-validated HRQOL measures typically include evaluation of minimal clinically important difference (MCID) scores, which go beyond tests of statistical significance and facilitate interpretation of the amount of change patients perceive to be beneficial (Guyatt, 2000; Jaeschke, Singer, & Guyatt, 1989).

Seven studies have been conducted on the impact of IV antibiotic treatment on HRQOL in patients with CF (Bradley, McAlister, & Elborn, 2001; Britto et al., 2002; Esmond, Butler, & McCormack, 2006; Munzenberger, Van Wagnen, Abdulhamid, & Walker, 1999; Orenstein, Pattishall, Nixon, Ross, & Kaplan, 1990; Wolter, Bowler, Nolan, & McCormack, 1997; Yi, Tsevat, Wilmott, Kotagal, & Britto, 2004). Overall, these studies have indicated improvements following treatment in several areas of functioning, such as physical, social, and symptom-problem domains (Munzenberger et al., 1999). Compared to healthy norms, studies have also demonstrated that PEs have negative effects on physical functioning, general health, and role functioning (Britto et al., 2002). Limitations of these studies included their relatively small or absence of pediatric samples (Esmond et al., 2006; Munzenberger et al., 1999; Orenstein et al., 1990), lack of CF-specific HRQOL measures (Bradley et al., 2001; Britto et al., 2002; Munzenberger et al., 1999; Orenstein et al., 1990; Wolter et al., 1997; Yi et al., 2004), use of measures (e.g., Quality of Well-Being Scale) that were developed and validated only for adults (Munzenberger et al., 1999; Orenstein et al., 1990), reliance on parent-proxy reports for children (Britto et al., 2002; Yi et al., 2004), and follow-up data collection occurring two months after treatment (Britto et al., 2002; Yi et al., 2004). The current study uses a prospective design with two well-validated pediatric HRQOL measures to build upon prior research in this chronic illness population.

Overall, these data suggested that generic domains of HRQOL improved following IV treatment of a PE; however, little is known about the impact of these treatments on CF-specific domains of HRQOL in children and adolescents. Thus, the purpose of the current study was to assess statistically and clinically meaningful changes on both generic and CF-specific HRQOL for children and adolescents treated with IV antibiotic therapy for a PE within a real-world clinical setting, as well as changes in their clinical status. Based on prior literature, HRQOL and clinical status (e.g., FEV₁% predicted and BMI) were expected to improve from pre- to post-IV antibiotic therapy for all children and adolescents on the Physical and Social scales of the PedsQL™ and the Physical, Social, Respiratory, Health Perceptions, Role, and Weight scales of the CFQ-R. Secondary exploratory aims included examining changes on other HRQOL domains, including Emotional, Body Image, Eating, Treatment Burden, Digestion, and Vitality scales of the CFQ-R.

Method

Participants

Participants in this study included 52 children and adolescents with CF admitted to two children's hospitals, Shands Hospital, University of Florida ($n = 25$) and Cincinnati Children's Hospital Medical Center ($n = 27$), for treatment of a PE. Inclusion criteria included: (1) a confirmed diagnosis of CF; (2) age 6–18 years; (3) IV antibiotic treatment prescribed for a PE, which was diagnosed based on symptoms, laboratory data, and clinical evaluation; (4) ability to complete the pre- and post-treatment assessments within the specified time frame (e.g., within 48 hours of admission); and (5) no impairments that would hinder the understanding and completion of the measures (e.g., developmental delay).

Seventy-one participants were approached to participate in this study. Nineteen participants were excluded for the following reasons: 12 did not wish to participate because they were too sick at the time of recruitment or were not interested in research and seven participants had unusable data (e.g., $n = 2$ invalid responses due to developmental delays, $n = 5$ participants who were initially hospitalized for a PE but had other complications (e.g., sinus infections) that resulted in long-term use of oral and IV antibiotics). This resulted in a final sample size of 52 participants and their families. Participants who were treated more than once for a PE during the data collection period were included only once in the study. Of note, this sample represents a majority of participants in the CF clinic who were treated for pulmonary exacerbations with IV antibiotics during the study. Demographic characteristics of the sample are presented in Table 1.

Measures

Demographic Information—A demographic questionnaire was completed by parents of children and adolescents 6–17 years of age or by the patient him/herself if age 18. This measure provided general information about the child's age, sex, and medical history, as well as parent demographics.

Pediatric Quality of Life Inventory (PedsQL™; Varni et al., 2001)—The PedsQL™ is a 23-item generic HRQOL measure designed for children and adolescents between 2 and 18 years of age. In the current study, the PedsQL™ Young Child Report (ages 5–7), Child Report (ages 8–12) and Teen Report (ages 13–18) were used. Although the items were similar, the language for each version was developmentally appropriate for the specified age-ranges. The PedsQL™ assesses several domains of functioning, including Physical, Emotional, Social, and School using a 5-point Likert scale (0 = never a problem to 4 = almost always a problem). Domain and Total scores range from 0–100, with higher scores representing better HRQOL. The PedsQL™ has demonstrated validity and reliability (Cronbach alpha's 0.68–0.83; Varni et al., 2001). Minimal clinically important difference (MCID) scores ranged from 4.36 (Total Score) to 9.12 (School Functioning) (Varni et al., 2001).

Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Modi & Quittner, 2003; Quittner et al., 2005; Quittner, Modi, Watrous, & Davis, 2003)—The CFQ-R is a disease-specific HRQOL measure designed for children, adolescents, and adults with CF. Two self-report versions of the CFQ-R were used in this study, the CFQ-R Child Version (6–13 years old) and the CFQ-R Teen/Adult Version (14 years and older). The CFQ-R Child Version consists of 8 scales: Physical, Emotional, Social, Body Image, Eating, Treatment Burden, Respiratory, and Digestion. The CFQ-R Teen/Adult Version consists of the same eight scales in addition to the following four scales: Role, Vitality, Health Perceptions, and Weight. The CFQ-R uses a 4-point Likert scale and produces scaled scores ranging from 0 to 100, with higher scores representing better HRQOL. Prior studies have successfully combined similar scales on the Child and Teen/Adult versions due to overlapping constructs and items (Palermo, Harrison, & Koh, 2006). Internal consistency coefficients ranged from .60 to .76 for the CFQ-R Child Version (Modi & Quittner, 2003) and .67 to .94 for the CFQ-R Teen/Adult Version (Quittner et al., 2005). MCID scores have been calculated for the Respiratory scale, indicating it is 5.0 points (Quittner et al., 2009).

Clinical Status—Pulmonary function tests were conducted using American Thoracic Society standards. Wang (Wang, Dockery, Wypij, Fay, & Ferris, 1993) and Hankinson (Hankinson, Odencrantz, & Fedan, 1999) equations were used to calculate forced Expiratory Volume in one-second ($FEV_{1\%}$ predicted) and forced expiratory flow 25 to 75% ($FEF_{25-75\%}$). For a subset of participants (i.e., Cincinnati site only because this data was not

collected at the University of Florida; $n = 27$), weight and height data were used to calculate body mass index (BMI in kg/m^2).

Procedure

The Institutional Review Boards at both sites approved the study protocols and consent forms. Participants who met the inclusion criteria were informed about the study after a decision was made to treat the PE with IV antibiotics. If the patient and family agreed to participate, verbal assent was obtained from children and adolescents, and informed consent was obtained from parents for children and adolescents ages 6–17. Informed consent was obtained from participants if they were 18 years of age.

Participants completed the pre-assessment during the first 48 h of the initiation of IV antibiotics. After this period, participants either remained in the hospital or went home on IV antibiotics, a decision that was made jointly by participants and the healthcare team in the context of their routine clinical care. At the pre-assessment, parents completed the demographic form and children completed the PedsQL™ and CFQ-R. The post-assessment for all participants occurred approximately 2 weeks after the initiation of IV antibiotics. For participants who were in the hospital, this took place within 48 h of hospital discharge and thus discontinuation of IV antibiotics. For participants who went home on IV antibiotics, routine follow-up care required participants to return to clinic 2 weeks after initiating IV antibiotic therapy and thus the post-assessment took place in the CF clinic. During the post-assessment, children completed the PedsQL™ and CFQ-R. Pulmonary function data and participants' weights and heights (Cincinnati site only) were also obtained from their medical records at both assessment points. A trained research assistant or principal investigator administered the measures and was available to answer questions at each assessment point. After completion of each assessment, participants were given a gift certificate to local stores as an appreciation of their time and participation in the study.

Statistical Analyses

Paired t -tests were conducted to examine changes in PedsQL™ and CFQ-R scales from pre- to post-treatment, as well as changes in clinical status (e.g., $\text{FEV}_{1\%}$ predicted and $\text{FEF}_{25-75\%}$, BMI). To control for Type I error rate, a Bonferroni correction was used; p values were set at .008 for the PedsQL™ (.05/6 scales = .008) and .004 (.05/12 scales = .004) for the CFQ-R to achieve statistical significance. Change scores were calculated to examine their relations to established MCID scores. Pearson correlation coefficients were calculated to assess the relations between changes in clinical status and changes on the PedsQL™ and CFQ-R scales. Statistical significance was identified as $p \leq .05$, unless otherwise specified.

Missing data were imputed using a single imputation method using S-PLUS software, version 8.0 and the Hmisc library of Harrell (2007). All participants completed the CFQ-R at the pre-assessment point; however, four participants were missing pre-assessment PedsQLs. Six participants were missing post CFQ-R (2 child and 4 teen/adult) and PedsQL™ measures. Based on the correlation between the pre-post measures and the correlation between clinical status and HRQOL measures, a predictive multivariable model was employed to impute missing values using a single imputation method. However, if *both* pre and post measures were missing (e.g., four participants were missing pre and post PedsQL™ and one was missing pre- and post-medical variables), imputation values were not used. For a two-tailed alpha of .05 and a sample size of 52, we had 94% power to detect a mean difference of 11 points on the primary HRQOL scale of interest (e.g. CFQ-R Respiratory scale).

Results

Site Differences

Chi-square and independent *t*-tests indicated no significant differences in sex ($\chi^2 (1, N = 52) = 2.0, p = .15.$), age in years ($t (50) = -.72, p = .47$), baseline FEV_{1%} predicted ($t (49) = 1.8, p = .07$), or race ($\chi^2 (1, N = 52) = 1.1, p = .58$) between the two sites; therefore, data from both sites were combined.

HRQOL Changes

Paired *t*-tests indicated no significant changes on PedsQL™ scales (See Fig. 1). However, significant improvements were found on the CFQ-R Respiratory ($t (51) = -4.4, p < .0001$) and Weight ($t (27) = -4.1, p < .0001$) scales (See Fig. 2). Statistically significant improvements were also found for FEV_{1%} predicted ($t (50) = -6.3, p < .001$), FEF_{25-75%} ($t (50) = -4.8, p < .001$), and BMI ($t (25) = -3.1, p < .001$) (See Fig. 3). HRQOL change scores were compared to previously reported MCIDs for the PedsQL™ and CFQ-R Respiratory scale. Results indicated that participants reported large, clinically significant differences on the CFQ-R Respiratory scale based on the established MCID (Mean change score = 11.7 points versus MCID = 5.0).

Relation between Clinical Health Status and HRQOL Changes

Change in FEV_{1%} predicted was significantly and positively correlated with changes on the CFQ-R Physical Functioning scale ($r = .35, p < .01$). Change in BMI was significantly and positively correlated with changes on the CFQ-R Weight ($r = .60, p < .05$) scale and the PedsQL™ Physical Functioning scale ($r = .39, p < .05$).

Discussion

To our knowledge, this is the first *prospective* study to demonstrate improvements following treatment for a PE on a disease-specific HRQOL in children and adolescents with CF. Specifically, children and adolescents reported improvements on the CFQ-R Respiratory and Weight scales. In addition, lung function and nutritional status improved after receiving IV antibiotic therapy for a PE. This demonstrated strong convergence between clinical health status measures and PROs, measured using a disease-specific tool. Results indicated that as respiratory symptoms improved, patients reported significant improvements on the disease-specific HRQOL measure. Similarly, as patients began feeling better, their appetites increased, leading to changes in weight and BMI, which were reflected on both the PedsQL Physical and CFQ-R Weight scales. These data build upon prior studies indicating that IV antibiotic therapy improves HRQOL.

Data from the current study also highlighted the sensitivity of the CFQ-R to detect change in comparison to the generic PedsQL™. The larger literature has also supported the use of disease-specific instruments when evaluating the results of interventions and/or treatments (Juniper et al., 1996; Kolotkin & Crosby, 2002; Le Pen, Levy, Loos, Banzet, & Basdevant, 1998). Our data on the effects of IV antibiotic therapy are the first to support these findings in children and adolescents with CF and suggest that use of a CF-specific measure provides more meaningful data than generic measures. Results from this study are encouraging because IV antibiotic treatment of a PE was associated with improvements not only in traditional clinical measures, such as pulmonary functioning, but also in symptoms reported by patients themselves on the CFQ-R. As previously mentioned, the FDA is currently encouraging the use of well-validated PROs, such as HRQOL, in clinical trials (U.S. Food and Drug Administration, 2006). There are few well-validated PROs in CF (Goss & Quittner, 2007); however, this study demonstrates the importance of their use to increase sensitivity and clinical utility.

Our findings were further supported by the application of the MCID value for each of the HRQOL measures. Our results were not only statistically significant, but also clinically meaningful based on the patient's report. This highlights the importance of using the MCID value in conducting patient-oriented clinical research rather than relying solely on statistical significance (Beaton, Boers, & Wells, 2002; Jaeschke et al., 1989). Given the challenges of obtaining large samples of patients with CF, use of the MCID value may allow studies to be adequately powered with fewer patients. Although no clinically significant changes were detected on the PedsQL™, the CFQ-R Respiratory scale demonstrated clinically meaningful improvements for children and adolescents following IV antibiotic treatment for a PE. This finding is important both for clinical decision-making and the evaluation of new treatments in clinical trials (Quittner, McCoy, & Montgomery, 2007).

This study is not without limitations. First, although sample size was relatively large when compared to similar studies (Britto et al., 2002), the addition of more patients would have increased the generalizability of the findings. Second, the sensitive time frame (i.e., 48 hours after IV initiation) and difficulty implementing the study in a real-world setting (e.g., obtaining consent from parents when they were present in the hospital, collecting data at a time convenient for families (e.g., not during airway clearance or pulmonary function tests)) resulted in missing data for some patients. This was addressed with the use of imputation techniques. Third, we did not assess whether patients with CF returned to their baseline pulmonary function value, which is an important goal for CF teams. Although determining baseline FEV_{1%} predicted can be quite difficult due to yearly declines, acquisition of bacteria, and individual differences, future studies would benefit from evaluating change in the context of baseline FEV_{1%} predicted. Fourth, a longitudinal follow-up of patients following IV treatment of a PE would improve our understanding of how health status, treatment decisions, and HRQOL impact each other across time. Finally, given the increasing shift toward treating patients with PEs at home with IV antibiotics, future randomized controlled trials examining the impact of treatment setting on PROs would be beneficial. Our small sample of children and adolescents treated in the home environment made it difficult for treatment setting comparisons.

Despite these limitations, overall, this study demonstrated the importance of measuring disease-specific HRQOL when evaluating the impact/effectiveness of medical interventions in children and adolescents with chronic illnesses, such as CF.

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Fig. 1.
PedsQL scores from pre to post IV antibiotic treatment

Fig. 2.
CFQ-R scores from pre to post IV antibiotic treatment. * Represents scales on the CFQ-R teen/
adult version only, † $p < .0001$

Fig. 3.
Health status indicators from pre to post IV antibiotic treatment. Significant differences were found for each health status indicator

Table 1Baseline demographic characteristics ($N = 52$)

Variable	Combined sample mean (SD)/percentage	UF sample mean (SD)/percentage	CCHMC sample mean (SD)/percentage
Sample size	52	27	25
Age	13.6 (3.7)	14.0 (2.8)	13.3 (4.4)
% male	54	64	44
% race			
Caucasian	94	92	96
African American	4	4	4
Hispanic	2	4	0
Length of IV treatment (days)	14.0 (4.9)	12.0 (4.7)	15.7 (4.5)
FEV ₁ % predicted (Pre) ^a	58.8 (21.5)	53.0 (14.8)	64.0 (25.5)
% disease severity ^a			
Normal	8	0	15
Mild (≥ 70)	23	24	26
Moderate (40–69)	44	57	41
Severe (≤ 39)	17	19	18
Treatment setting			
Hospital	71	96	48
Home	29	4	52

UF University of Florida, CCHMC Cincinnati Children's Hospital Medical Center

^a $n = 4$ (8%) of patients had pulmonary function tests missing at baseline (prior to initiation of IV antibiotic therapy)