Original Article

The Association Between Pain and Clinical Outcomes in Adolescents With Cystic Fibrosis

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Abstract

Context. Pain is a common problem in patients with cystic fibrosis (CF) and in adults is associated with lower quality of life and more pulmonary complications. Less is known about the impact of pain in adolescents with CF.

Objectives. This study aimed to describe pain in an adolescent CF population and to determine if pain at baseline is associated with lower health-related quality of life (HRQoL) and worse pulmonary outcomes at six-month follow-up.

Methods. We administered surveys at baseline and at six months to CF patients aged 12 to 20 years. Analyses included Wilcoxon log-rank tests, Spearman correlations, and linear and logistic regressions.

Results. Seventy-three patients (86.9%) completed the baseline questionnaire and 53 patients (63.1%) completed the six-month follow-up questionnaire. Mean age was 15.6 ± 2.5 and mean FEV_1 was $79 \pm 26\%$ predicted; 89% of patients reported pain in the three months before the survey, but in most it was short lived and mild to moderate in severity. Abdominal pain was the most common location. Pain was associated with increased pulmonary exacerbations (odds ratios = 1.99 for every one-point increase on a composite pain scale, $P = 0.03$) and with lower HRQoL.

Conclusions. Pain in adolescents with CF is associated with lower HRQoL and more pulmonary exacerbations. Greater efforts are needed to manage pain in this population and to determine if treatment of pain improves other outcomes. J Pain Symptom Manage 2016;52:681−687. © 2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic disease in Caucasians, affecting approximately 30,000 Americans and 70,000 people worldwide.[1] Although survival has improved dramatically, over half of patients with CF are 18 years and younger and suffer from many debilitating symptoms and problems including cough, dyspnea, diabetes, and fat malabsorption.[2] Although CF is not commonly thought of as a painful disease, there have been multiple studies published over the past decade describing a high prevalence of pain in individuals with CF.[3−12] The largest study to date found that 94% of adult patients reported pain in the previous two months and that one-third of patients rated it as severe.[4]

Although there is increasing recognition that pain is a common problem in CF, there is relatively little

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known about factors associated with pain and whether pain is independently associated with poor clinical outcomes in children and adolescents with CF. We previously published a study of pain in adults with CF and found that pain was associated with anxiety, depression, and lower quality of life.[13] Additionally, pain was associated with a higher risk of pulmonary exacerbations and death. It is unknown whether these findings hold true in a pediatric CF population, in which lung disease tends to be milder and co-morbid chronic medical problems are less prevalent.

The goals of this study were to describe the prevalence, severity, and location of pain in a pediatric CF population. Additionally, we hypothesized that increased levels of pain at baseline would be associated with lower health-related quality of life (HRQoL) and more pulmonary exacerbations at the six-month follow-up.

Methods

This study was approved by the Johns Hopkins Medicine Institutional Review Board (NA_00027981). Subjects consented to taking part in this study. The study was conducted between October 2011 and August 2012. Individuals with CF followed in the Johns Hopkins Pediatric CF program between ages 12 and 20 were included. Subjects were excluded if they were experiencing an increase in pulmonary symptoms. A computer-based survey was administered during clinic visits at baseline and again at a six-month follow-up visit. The two surveys contained the same questions.

Questionnaires

The survey was programmed into Survey Monkey® and patients completed the survey on computers in the clinic area. This was frequently done at the beginning of a clinic visit, but this was not protocolized. The questionnaire contained 188 items including demographic questions, questions about school and work, and 15 questions about pain. The pain questions were adapted from two sources, a previously used questionnaire by Palermo et al.[8] and the Brief Pain Inventory (BPI).[14] Table 1 lists examples of some of the pain questions.

The BPI is an assessment of pain that was originally developed for cancer patients to evaluate pain severity and to determine if pain interfered with daily life.[15] It has since been validated in patients without cancer.[16] The BPI asks patients if they have had pain in the past week, if they have pain most days for the past six months, and asks the patients to quantify their pain on a scale of 0–10, 10 being pain "as bad as it could be." The BPI also asks patients on a scale of 0 to 10, 10 being "completely interferes," how much pain interferes with their life, including general activity, mood, relationships, sleep, and social activities. As done in previous studies using the BPI,[14] we summarized pain rating into a composite pain score that included mean of the lowest pain and average pain in the previous seven days. We also performed analyses using average pain in the last seven days and overall worst pain and obtained similar scores. Unless specified otherwise, the pain ratings in the results are the composite pain score. To summarize and categorize pain severity, we report mild, moderate, and severe pain. This corresponds to numeric scores of 0–3, 4–6, and 7–10.[17,18]

Other elements of the questionnaire were the Pain Catastrophizing Scale, which is a 13-question assessment with three different categories: rumination, magnification, and helplessness.[19] The assessment evaluates the emotional response to pain and describes how likely an individual is to respond negatively to pain.

Cystic Fibrosis Questionnaire-Revised. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a CF-specific, validated scale that measures HRQoL on both generic and disease-specific domains.[20] There are multiple versions of the CFQ-R including one for patients aged 14 years and older and one for patients aged 6 to 13 years. We administered different versions based on the patient's age. The domains in the two versions are different and we report the eight domains that overlap between the two versions. We were particularly interested in the respiratory subscale because it has been used frequently as an outcome in clinical trials and the digestive symptoms subscale because we hypothesized it would be lower, i.e., indicative of worse digestive symptoms, in patients with abdominal pain related to malabsorption or distal intestinal obstruction syndrome.

Table 1
Examples of Pain Questions Used in the Study

Question
1. In the past three months how often have you had aches or pains?
2. Which part of your body do you experience the most problems with aches or pains?
3. When you have aches or pain, how much hurt do you usually have
4. What is your pain level at the present time, that is right now?
5. During the past week, on average, how severe was your pain?
6. During the past week how severe was your worst pain?
7. During the past week what was the lowest level of your pain?

Question 1 possible responses ranged from not at all to every day. Questions 3–7 possible responses ranged from 0 to 10.

Functional Disability Index. The functional disability index (FDI)[21] is a 15-item assessment of function across a wide variety of activities over the previous 2 weeks. The degree of difficulty for each item is rated on a scale from 0 (no trouble) to 4 (impossible).

Clinical Outcomes

The electronic patient medical record was reviewed to assess FEV_1 at study entry and at the time of six-month follow-up. Pulmonary exacerbations, defined as the use of an acute course of antibiotics in the setting of increased pulmonary symptoms, were recorded over the period from baseline to six-month follow-up. Additionally, we recorded pulmonary exacerbations treated with intravenous antibiotics and pulmonary exacerbations treated in the hospital during the six months of follow-up.

Data Analysis

Summary statistics are represented as means ± SD or medians with interquartile range. Bivariate analyses were performed using Wilcoxon log-rank tests, Spearman correlations, and linear and logistic regressions. Logistic regression models were used to analyze clinical outcomes including HRQoL and exacerbations. Multivariable models included factors found to be significant on univariate analysis. Age and gender were included in the models because of their perceived importance,[22,23] regardless of their statistical significance in univariate analyses. A *P*-value < 0.05 was considered statistically significant. Odds ratios (ORs) are presented with 95% confidence intervals. Statistical analyses were performed with STATA Statistical Software: release 12.1 (STATACorp, College Station, TX).

Results

Seventy-three of 84 eligible patients completed the baseline questionnaire (86.9% response rate) and 53 patients (63.1%) completed the six-month follow-up questionnaire. The most common reason cited for not participating was lack of time. Participants and nonparticipants had similar age distributions, but nonparticipants were more likely to be women; 83% of eligible women agreed to participate, compared with 97% of eligible men. This bordered on being statistically significant with a *P*-value of 0.051. The mean age of participants was 15.6 ± 2.5 years and slightly more than half were women. As expected in CF, the vast majority of the study population was Caucasian. The mean lung function was mildly reduced with a mean FEV_1 of 79 ± 26% predicted, but the study did include patients with a wide range of lung disease severity. The FEV_1 percent predicted ranged from 22% to 125%. Seventy-five percent of the study group experienced at least one acute pulmonary

exacerbation during the follow-up period. The patient characteristics appear in Table 2.

Pain was common in this pediatric CF population; at baseline, 89% reported pain, other than "every day kinds of pain," in the previous three months. The phrase "every day kinds of pain" is the wording used in the BPI.[14] However, in 80% of those reporting pain, it was short lived, and in most, it tended to be mild to moderate in severity: 43% rated pain levels between 0 and 3 and 50% rated it between 4 and 6 on the composite pain score. Figure 1 shows rating of average pain over three months. Similar to ratings of pain over the past seven days, the three-month recall showed pain ratings clustered in the mild-to-moderate range; 51% reported that pain lasted less than an hour per day and 29% said it lasted for a few hours per day. Pain occurred relatively infrequently (43% reported pain less than once a month, 23% had pain one to three times per month, and 35% had pain once a week or more). At baseline, the locations described as causing the most problems with pain were the abdomen (42.0%), head/sinuses (31.9%), joints (18.8%), chest (10.1%), back (5.8%), and muscles (2.9%; Fig. 2). Figure 1 also shows pain ratings at baseline and at six-month follow-up. The ratings within individuals did not change significantly over time. Additionally, change in pain scores over the study period was not associated with other outcomes, such as HRQoL.

There was a trend for increased pain with lower FEV_1 (Spearman Rho = −0.22, $P = 0.06$) and higher pain in women (average pain in women was 1.49 vs. 1.07 in men, $P = 0.08$); however, there were no demographic or illness characteristics significantly associated with the presence of pain. Pain was not associated with CF genotype or pancreatic insufficiency.

Pain, Disability, and Daily Activities

In response to a question asking to what extent pain prevents usual activities, with 0 indicating that pain does not limit any activity and 10 indicating that pain limits all activities, 19.4% of patients reported a score of 4 or higher. Pain was also associated with higher scores on the FDI. A one-quartile increase in average

Table 2
Patient Baseline Characteristics

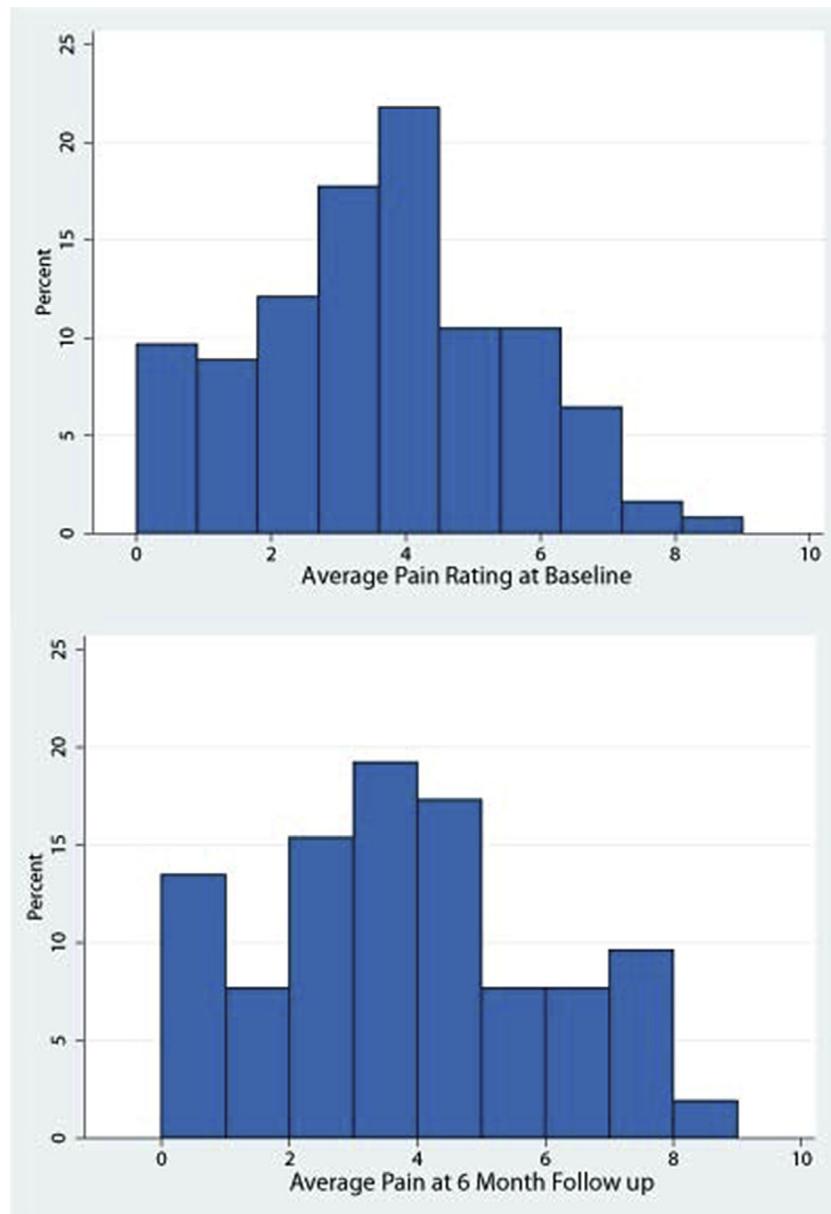| Characteristics	Result
Age, mean	15.6 ± 2.5
Female (*n, %*)	41 (56.2%)
Caucasian race (*n, %*)	63 (86.3%)
F508 del genotype (*n, %*)	41 (56.2%)
Pancreatic insufficient (*n, %*)	70 (94.6%)
Mean FEV_1 (L)	2.38 ± 0.95
FEV_1 percent predicted	79.3 ± 26.0
CF related diabetes mellitus (*n, %*)	11 (14.9%)
Prescribed antidepressant (*n, %*)	4 (5.5%)

Fig. 1. Average pain severity over three months at baseline and six-month follow-up. These histograms are a recall of pain severity over the past three months on a scale from 0 to 10 with "0" being no pain and "10" being the worst possible pain. The top graph is from the baseline survey and the bottom graph represents the six-month follow-up survey.

pain was associated with a 0.9-point increase in the FDI (95% confidence interval 0.02–1.79; $P = 0.045$). Patients who reported missing school had higher pain scores than those who did not miss school. For example, 36.4% of those who missed school were in the highest quartile of average pain scores, compared with 15.7% in those who did not miss school, $P = 0.02$.

Effects of Pain on Clinical Outcomes

Patients with higher baseline pain scores were significantly more likely to experience an acute pulmonary exacerbation requiring intravenous antibiotics during the 6-month follow-up period. Table 3 lists the results

of multivariate logistic regression. After adjusting for FEV_1, age, and gender, there was nearly a twofold higher risk of a pulmonary exacerbation for each one-point increase in the composite pain score (OR = 1.99; $P = 0.029$). Pain scores were also associated with an increased risk of subsequent hospitalization for pulmonary exacerbation (OR = 1.59, $P = 0.026$), although this was no longer significant after adjusting for FEV_1, age, and gender.

Health-Related Quality of Life

Higher levels of pain at study entry were associated with lower HRQoL at follow-up (Table 4). Of the eight
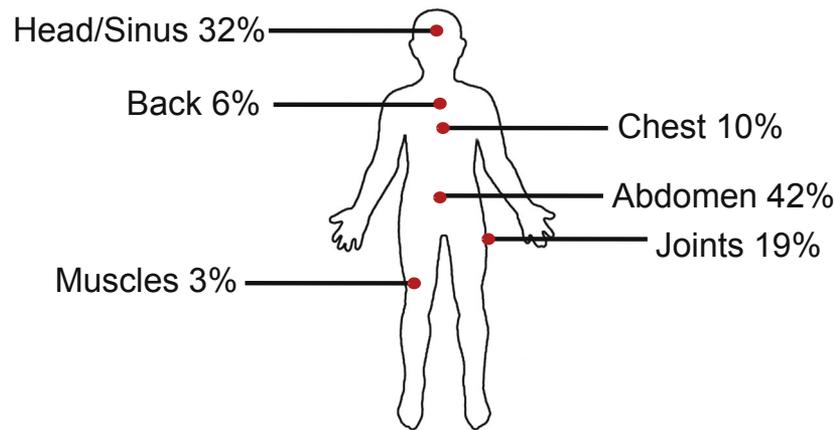
Fig. 2. Distribution of pain in adolescent cystic fibrosis.

domains in the children's version of the CFQ-R, there were statistically significant associations between pain and the physical, emotional, body image, and digestion domains but not the respiratory symptom scale.

Pain Catastrophizing

Higher total scores on the Pain Catastrophizing Scale were significantly associated with higher composite pain ratings (Spearman rho = 0.51, $P < 0.001$).

Discussion

This study demonstrated that pain is common in pediatric CF patients and interferes with daily activities, affects HRQoL, and increased frequency of pulmonary exacerbations. Indeed, the odds ratio for acute pulmonary exacerbations requiring IV antibiotics was nearly doubled for each point on a composite score of pain. However, adolescents with CF differ from adults, in that pain tends to be less severe, is shorter in duration, and is primarily centered in the abdomen. These results have important implications in patient assessment, medical management, and outcome.

Although most previous studies of pain in CF have focused on adults,[24] our findings of pain prevalence are consistent with the previous reports of pediatric CF populations. Sermet-Gaudelus et al.[12] reported that 59% of children with CF had at least one episode

of pain in the previous month. Similarly, we found that 58% of our cohort had pain one or more times per month. Likewise, Koh and colleagues found a relatively similar prevalence with 46% of children reporting pain at least once per week.[7,8] Using daily diaries, Blackwell and Quittner found that 76% of adolescents had episodes of pain.[10] In contrast, a study by Munck et al.[25] found a very low incidence (6%) of recurrent abdominal pain in children with CF. At face value, this may appear to be entirely inconsistent with our findings and those of others, but the study by Munck used a strict definition of recurrent abdominal pain, "at least three bouts of pain, severe enough to affect activities, over a period of not less than three months, with attacks in the year preceding the examination," which may explain the differences.

Similar to the Sermet-Gaudelus and Blackwell studies, we found that abdominal pain was the most common site of pain in children with CF. Compared with a previous study at our site in adults with CF,[13] pain in the pediatric population seems to be less severe and shorter in duration than the adults. Interestingly, the prevalence of pain in adolescents with CF does not appear to be dramatically different from the general pediatric population. Perquin et al.[9] reported that 54% of children in The Netherlands reported pain in the previous three months.

Although pain appears to be less severe in the pediatric population than in adults, it is still strongly associated with poor clinical outcomes including lower HRQoL and increased pulmonary exacerbations. Pain at study entry was significantly associated with the respiratory symptom scale of the CFQ-R (data not shown), but baseline pain was not associated with the respiratory subscale of the CFQ-R at the six-month follow-up. This may have occurred because we did not administer surveys to patients who were experiencing an increase in respiratory symptoms. Therefore, we selected subjects with stable pulmonary

Table 3
Association Between Baseline Pain and Pulmonary Exacerbations in the Following Six Months

Variables	Odds Ratio	95% Confidence Interval	*P*-Value
Pain score	1.99	1.07–3.68	0.030
FEV1	0.06	0.01–0.31	0.001
Age	1.78	1.22–2.60	0.003
Gender	0.70	0.14–3.41	0.66

Pain score is a composite score averaging the lowest and average pain scores over the previous seven days. These are the results of multivariable logistic regression adjusting for FEV_1, age, and gender. This shows nearly a twofold higher risk of a pulmonary exacerbation for each one-point increase in the composite pain score.

Association Between Pain Score and Health-Related Quality of Life

CFQ-R Domain	β Coefficient	95% CI	*P*-Value
Physical functioning	−4.44	−7.6 to −1.3	0.006
Emotional functioning	−4.58	−7.6 to −1.6	0.003
Body image	−7.69	−12.2 to −3.1	0.001
Respiratory symptoms	−0.82	−4.4 to 2.7	0.646
Digestion symptoms	−4.19	−8.2 to −0.14	0.043
Eating	−2.53	−6.2 to 1.17	0.18
Treatment burden	−4.63	−10.2 to 0.90	0.098
Social functioning	−2.69	−6.5 to 1.2	0.167

CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval.

These are results from unadjusted linear regression measuring the association between composite pain score at baseline and the domains or symptom scales of the CFQ-R at six-month follow-up.

symptoms. Future investigations need to determine the mechanism linking pain and CF pulmonary exacerbations. Blackwell and Quittner found an association between pain and lower treatment adherence,[10] which could be one potential explanation for our finding, given that poor adherence may lead to exacerbations. Alternatively, pain in CF could be a marker of systemic inflammation and disease activity. Pain could simply be a characteristic of more symptomatic patients who are more likely to present to clinical attention and ultimately be treated with antibiotics for pulmonary exacerbations. We think pain is more likely linked in a physiological pathway to exacerbations, as it is our clinical experience that many patients, who do not experience severe pain most of the time, consistently develop pain at the time of exacerbations. This, however, contrasts with the findings of Kelemen et al.,[11] who found lower pain severity at the time of exacerbations. That study was limited though, in that fewer than half of the patients studied at baseline were evaluated at the time of an exacerbation.

Pharmacologic treatment of pain in CF is a challenging area, particularly in adolescents.[26,27] Although opioid analgesics are effective, they have a number of undesirable properties including constipation and suppression of cough.[28] Further investigation into methods to manage pain in CF including non-opioid analgesics, psychological counseling, physical therapy, acupuncture, and other nontraditional approaches should be considered.

Our study population appears to be representative of our general CF population, with a broad age range from 13 to 18, good representation of both genders, and FEV1 ranged from 22% predicted to 125%. Additionally, our study used well-validated instruments, which were age appropriate. Nevertheless, this study was limited by its relatively small sample size and single-site design. Only 53 patients completed the six-month follow-up visit, and therefore, the generalizability cannot be guaranteed. We did not specifically inquire about treatment-related pain and, therefore, cannot distinguish whether the pain described is due to treatments or more general pain. However, abdominal pain was the most common location of pain,

which seems unlikely to be triggered by the typical CF treatments. It would be helpful to know more details about how patients cope with pain and about their interactions with their health care providers regarding pain. Although this was not captured in the present study, we are in the process of carrying out a qualitative study describing the experiences of patients with CF who report higher levels of pain.

We have confirmed that pain is highly prevalent in pediatric CF patients and that abdominal pain is the most common site of pain. Additionally, pain in this group tends to be less severe and shorter lived than adults with CF. Importantly, pain has a negative impact on daily activities, HRQoL, and pulmonary health, as indicated by increased pulmonary exacerbations. There is a dearth of literature on treating pain in CF and greater efforts need to be made to develop a rational, evidence-guided approach to this problem. We, and others, have assessed the prevalence and impact of pain in relatively small studies at single centers. It will be important moving forward to begin evaluating pain and its effects on HRQoL, psychological distress, and other health parameters on a national level. The CF Foundation's Patient Registry would be one potential vehicle, which could be used to collect information on pain in the vast majority of individuals with CF in the U.S.

Disclosures and Acknowledgments

References

1. Cystic Fibrosis Foundation Patient Registry. 2012 Annual report. Bethesda, MD 2013.

2. Davis PB. Cystic fibrosis since 1938. Am J Respir Crit Care Med 2006;173:475−482.

3. Chastain D, Cook A. Chronic pain in CF: associated beliefs and behaviors. Pediatr Pulmonol 2000;30:116−117.

4. Festini F, Ballarin S, Codamo T, Doro R, Loganes C. Prevalence of pain in adults with cystic fibrosis. J Cyst Fibros 2004;3:51−57.

5. Flume PA, Ciolino J, Gray S, Lester MK. Patient-reported pain and impaired sleep quality in adult patients with cystic fibrosis. J Cyst Fibros 2009;8:321−325.

6. Hubbard PA, Broome ME, Antia LA. Pain, coping, and disability in adolescents and young adults with cystic fibrosis: a Web-based study. Pediatr Nurs 2005;31:82−86.

7. Koh JL, Harrison D, Palermo TM, Turner H, McGraw T. Assessment of acute and chronic pain symptoms in children with cystic fibrosis. Pediatr Pulmonol 2005;40:330−335.

8. Palermo TM, Harrison D, Koh JL. Effect of disease-related pain on the health-related quality of life of children and adolescents with cystic fibrosis. Clin J Pain 2006;22: 532−537.

9. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, et al. Pain in children and adolescents: a common experience. Pain 2000;87:51−58.

10. Blackwell LS, Quittner AL. Daily pain in adolescents with CF: effects on adherence, psychological symptoms, and health-related quality of life. Pediatr Pulmonol 2015; 50:244−251.

11. Kelemen L, Lee AL, Button BM, et al. Pain impacts on quality of life and interferes with treatment in adults with cystic fibrosis. Physiother Res Int 2012;17:132−141.

12. Sermet-Gaudelus I, De Villartay P, de Dreuzy P, et al. Pain in children and adults with cystic fibrosis: a comparative study. J Pain Symptom Manage 2009;38:281−290.

13. Hayes M, Yaster M, Haythornthwaite JA, et al. Pain is a common problem affecting clinical outcomes in adults with cystic fibrosis. Chest 2011;140:1598−1603.

14. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23:129−138.

15. Cleeland CD. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. Issues in pain management. Advances in pain research and therapy. New York: Raven Press, 1989:391−403.

16. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20:309−318.

17. Palos GR, Mendoza TR, Mobley GM, Cantor SB, Cleeland CS. Asking the community about cutpoints used to describe mild, moderate, and severe pain. J Pain 2006;7: 49−56.

18. Jensen MP, Smith DG, Ehde DM, Robinsin LR. Pain site and the effects of amputation pain: further clarification of the meaning of mild, moderate, and severe pain. Pain 2001;91:317−322.

19. Sullivan M, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7: 524−532.

20. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest 2005;128:2347−2354.

21. Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. J Pediatr Psychol 1991;16:39−58.

22. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10: 447−485.

23. Turk DC, Okifuji A, Scharff L. Chronic pain and depression: role of perceived impact and perceived control in different age cohorts. Pain 1995;61:93−101.

24. Havermans T, Colpaert K, De BK, Dupont L, Abbott J. Pain in CF: review of the literature. J Cyst Fibros 2013;12: 423−430.

25. Munck A, Pesle A, Cunin-Roy C, et al. Recurrent abdominal pain in children with cystic fibrosis: a pilot prospective longitudinal evaluation of characteristics and management. J Cyst Fibros 2012;11:46−48.

26. Craig KD, Lilley CM, Gilbert CA. Social barriers to optimal pain management in infants and children. Clin J Pain 1996;12:232−242.

27. Committee on Psychosocial Aspects of Child and Family Health, Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics 2001;108:793−797.

28. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11: S105−S120.