Laryngoscope Investigative Otolaryngology

Clinical Chronic Rhinosinusitis Outcomes in Pediatric Patients with Cystic Fibrosis

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Objectives: Chronic rhinosinusitis and nasal polyposis are common conditions in cystic fibrosis (CF). Approximately 2–3% of pediatric CF patients per year have sinus disease requiring surgery. It has been well established that there is a significant negative impact on quality of life associated with chronic rhinosinusitis (CRS) in the non-CF patient population. However, the impact of CRS on the pediatric CF population remains uncertain. The purpose of this article is to review the current state of outcome measures for CRS in pediatric CF patients.

Data Sources: PubMed and EMBASE literature review

Methods: PubMed and EMBASE electronic databases were searched using Boolean searches that incorporated mesh headings and plain language for quality of life, symptom evaluation, pediatric patients, and sinusitis/rhinosinusitis. Studies were included if the study primarily evaluated a pediatric Cystic Fibrosis-Chronic Rhinosinusitis (CF-CRS) population and the primary outcome measure was quality of life evaluation.

Results: The search yielded 34 unique articles. A total of 7 articles met inclusion criteria

Conclusions: Despite the high frequency of chronic rhinosinusitis in the pediatric CF patient population, its impact on quality of life is not well understood. Currently there is a lack of a validated disease specific quality of life instruments available to assess the impact of CRS on the pediatric CF patient population.

Key Words: Chronic sinusitis, cystic fibrosis, patient reported outcomes, quality of life.

Level of Evidence: 5.

INTRODUCTION

Individuals with cystic fibrosis (CF) have an incidence of chronic rhinosinusitis (CRS) approaching 100%, which is often associated with nasal polyposis (6–48%).[1–5] However, data from the US Cystic Fibrosis Foundation (CFF) registry indicates that only 2–3% of pediatric patients per year have sinus disease requiring surgery.[5] Other single-center studies have documented that approximately 10–20% of CF patients require surgical management of their sinus disease.[6] Despite the high prevalence of CRS in the CF population, little is known about the optimal treatment, indications for surgery, and outcomes of treatment for CF CRS, leading to wide variation in practice patterns. A recent study demonstrated that there is large variation in the frequency of sinus surgery (1–24%) in 29 of the largest US pediatric hospitals.[7] The reason for this variation is uncertain.

Health related quality of life outcome measures have become an increasingly important part of health care delivery and our evaluation of the care that is delivered by our system. Increasingly, clinical trials require patient-reported outcome measures (PROs) to be part of primary or secondary endpoints. However, the instruments used for these purposes vary greatly and there is no "gold standard" for how these outcomes are measured or reported. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is the most widely used PRO for cystic fibrosis.[8–13] This is a disease-specific health-related quality-of-life instrument (HRQOL) based on the 2 weeks prior to the patient encounter. There are 4 versions of the CFQ-R that include the ages 3–6, 6–13, and 14 through adulthood. Interviewer format is utilized until the age of 12. The questionnaire measures several domains including physical functioning, vitality, health perceptions, respiratory symptoms, treatment burden, role functioning, emotional functioning, and social functioning. There are no specific domains in this instrument evaluating sinusitis.

Currently, numerous health related quality of life instruments evaluating overall health in the general population exist. The SF-36[14] and SF-12[15] both measure physical and mental health, and the SF-10 health survey for children[16] is a parent-completed survey that contains 10 questions adapted from the Child Health Questionnaire (CHQ).[17] The SF-10 provides coverage across a wide range of domains, and is scored to produce physical and psychosocial health summary measures.[18] The Health Utilities Index-3 (HUI-3),[19] a comprehensive multi-attribute (generic) health status classification system, has previously been validated in the pediatric

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Editor's Note: This Manuscript was accepted for publication 4 March 2017.

No financial disclosures.

No conflicts of interest.

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DOI: 10.1002/lio2.78

TABLE I.
Summary of Commonly Used CRS QOL Instruments.

Author	Type	Study Purpose	Patients (n)	Ages	Pre- and Post-operative comparison	QOL measure	Duration of benefit measured	Results
Jones et al.	Retrospective review and phone call survey	Evaluate pre- and post-surgical symptom scores	17 16 pediatric 1 adult	3–30	Yes	Non-validated symptom questionnaire	No	Conclusion: that there was postoperative improvement in symptoms. No statistical analysis
Friedman et al.	Prospective data collection	Compare QOL scores with pulmonary function	51	7–20	No	SNOT-16	No	SNOT-16 score was predictive of FEV1 in patients <12 years of age
Keck et al.	Prospective data collection	Compare pre- and post-surgical symptom scores	26	3–33	Yes	Non-validated symptom score	No	Improved symptoms following treatment
Taylor et al.	Prospective cohort study	Compare pre- and post-surgical symptom scores	10 CF patients 11 non-CF	5–18	Yes	PedsQLTM SNOT-16 SN-5	No	Preoperative impairment; improvement with sinus surgery
Thamboo et al.	Cross sectional study	SNOT-22 to predict presence of polyps	37	6–18	No	SNOT-22 UPSIT	No	SNOT-22 score may assist is predicting presence of polyps
Wentzel et al.	Prospective data collection	Comparison of SN-5 score with frequency of sinusitis exacerbation or antibiotic use, missed days of school, and missed activities	50	2–12	No	SN-5	No	Worse SN-5 scores were associated with more frequent sinusitis exacerbations, antibiotic use, missed days of school, and missed activities
Chan et al.	Prospective data collection	Comparison of CRS diagnosis with SN-5 scores	47	2–20	NO	SN-5	No	High prevalence of CRS with low impact on QOL

QOL = quality of life; SNOT = sinonasal outcomes test; CRS = chronic rhinosinusitis; SN-5 = sinonasal-5; UPSIT = university of pennsylvania smell identification test; CF = cystic fibrosis; PedsQLTM = pediatric quality of life inventory TM.

TABLE II.
Summary of Articles Evaluating Quality of Life in CF-CRS Patients.

Validated Instrument	Age Group	Reporter	Design	Validated in CF patient population
Sinonasal-5	2–12	Parent Reported	-7 point response to 5 symptoms -Average score -10 Point Visual analogue scale for overall QOL	No
Sinonasal Outcomes Test-20	≥18	Patient reported	-20 question CRS related questions -0–5 score -Average Magnitude score -Top 5 ranked by reporter	No
Sinonasal Outcomes Test-16	≥18	Patient reported	-4 questions less than SNOT-20 for research purposes -Same scoring as SNOT-20	No
Sinonsal Outcomes Test-22	≥18	Patient reported	-SNOT-22 with additional questions for nasal obstruction and smell disturbance -0–5 score -Average magnitude score -Top 5 are not ranked	No

CF = cystic fibrosis; CRS = chronic rhinosinusitis; QOL = quality of life; SNOT-20 = sinonasal outcome test-20; SNOT-22 = sinonasal outcomes test-22.

population for numerous disease states and is both reliable and generalizable in pediatric patients with acute illness. The HUI-3, for instance, assesses domains including vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. However, generic HRQOL instruments suffer from an important shortcoming, namely that they are designed to be applicable to a wide variety of populations with many different underlying conditions. As a result, they may not be sufficiently sensitive for capturing meaningful differences among patients with a specific condition or chronic symptoms.

Within the otolaryngology subspecialty, several HRQOL instruments have been validated and are used regularly to evaluate patients with CRS (Table I). The Sinonasal Outcome Test (SNOT-22) is a HRQOL instrument that has been previously validated.[20] This instrument was developed to assess patient-reported outcomes in the chronic rhinosinusitis (CRS) adult patient populations. The SNOT-22 evaluates HRQOL in such areas as physical problems, functional limitations and emotional consequences. Scoring of each question centered on a problem ranks on a 5-point scale (0 = no problem to 5 = problem is as bad as it can get) and is evaluated based on the problems from the previous 2-week period.

While several studies have been conducted to assess the reliability and generalizability of HRQOL instruments developed for adult otolaryngology patients, very few instruments appropriately evaluate the pediatric population. One scale, The Sinonasal-5 (SN-5) survey, has been used to evaluate the severity of sinonasal disease in patients between the ages of 2 and 12.[21] This survey is comprised of 5 domains including sinus infection, nasal obstruction, allergy symptoms, emotional distress, and activity limitations. Within each domain are symptom clusters that are scored on a 7-point scale (1 = none of the time to 7 = all of the time). Additionally, the survey asks parents to rate the overall quality of life of their child on a scale from 0 to 10, with 0 representing "worse possible quality of life" and "10 representing the best quality of life."

CRS has been clearly demonstrated to have a negative impact on the quality of life in the non-CF patient population. In fact the impact has been shown, in adult patients, to rival that of congestive heart failure and chronic kidney disease.[22] In pediatric patients with CRS it has been demonstrated that CRS also has a significant negative impact on health related quality of life.[17] However, the impact of CRS on the pediatric CF population is not as well defined.

The purpose of this paper is to review current outcome measures for CRS in pediatric CF patients and to highlight the gaps in these measures that currently exist.

METHODS

PubMed and EMBASE electronic databases were searched using Boolean searches that incorporated mesh headings and plain language for quality of life, symptom evaluation, pediatric patients, and sinusitis/rhinosinusitis. A single author reviewed the results of these searches to determine applicability to the review topic. Pediatric was defined as patients ≤18. Studies were included if the study primarily evaluated a pediatric CF-CRS population and the primary outcome measure was quality of life evaluation.

RESULTS

The PubMed and EMBASE search generated a total of 34 unique articles. A total of 7 articles met criteria for inclusion. (Table II) The articles not included in this review were studies of adult patients, non-cystic fibrosis

patients, did not have quality of life as a primary outcome measure, or were non-chronic rhinosinusitis related.

Jones et al. in 1993 attempted to evaluate the correlation between sinus surgery and symptoms in a group of pediatric patients with cystic fibrosis. In this study, 16 pediatric patients and 1 adult patient were contacted by phone 5–70 months following endoscopic sinus surgery. They were asked to report frequency of headaches per month pre- and post-intervention, as well as rate the symptoms of nasal obstruction, nasal discharge, postnasal drip, halitosis, and cough. These symptoms were rated and scored as occurring constantly (4 points), often (3 points), seldom (2 points), and never (1 point). The study reported that there was a decrease in the symptom domains nasal obstruction, purulent nasal discharge, and postnasal drip. However, no statistical analysis of the pre- and postoperative scores was performed. The conclusion of the paper, based on the findings, was that endoscopic sinus surgery improved quality of life in the study patient population.[23]

The relationship between sinus disease and reactive airway disease has been well established.[24] This relationship in cystic fibrosis is not as well defined. Friedman and Stewart in 2006 evaluated the link between sinus quality of life and pulmonary function.[25] In this study the Sinonasal Outcomes Test-16 (SNOT-16) was used to evaluate symptoms in a CF population aged 7–20 years (mean 11.7). SNOT-16 is an instrument developed by Piccirillo et al. and subsequently validated in an adult population by Anderson et al.[26] This instrument evaluates symptoms and the social and emotional consequences of the patient's rhinosinusitis. A higher score indicates worse impact on quality of life and functional status. Using univariate correlation and multivariable regression they attempted to demonstrate a link between SNOT-16 scores and forced expiratory volume in one second (FEV1). When the population was taken as a whole there was no correlation. However, when dividing the patient population into ages <12 and ≥ 12 they found that SNOT-16 score was predictive of FEV1 in children <12 ($p=.012$). In younger children a worse SNOT-16 score was associated with lower FEV1. The authors concluded, based on the results of this study, that the SNOT-16 could be used to assess sinus interventions on pulmonary status.

In 2007 Keck et al. evaluated a group of 26 cystic fibrosis patients with CRS. The average age was 3–33. Pre and postoperative symptom scores were evaluated using a nonvalidated 6-point Likert scale. There were statistically significant improvements pre and post operatively for the domains: facial pain ($p = .003$), headache ($p = .001$), nasal obstruction ($p \leq .001$), post nasal drip ($p \leq .001$), anterior rhinorrhea ($p = .002$), and total rhinosinusitis symptom score ($p \leq .001$). The conclusion of this paper was that endoscopic sinus surgery provided significant relief from nasal and facial symptoms associated with CRS.[27]

Taylor et al. in 2014 evaluated both CF and non-CF CRS. In this study, 10 CF patients and 11 non-CF patients were included. Each parent completed Pediatric Quality of Life Inventory TM (PedsQLTM), SNOT-16 at 2 weeks prior to surgery and at 1–3 months post-operatively. The Peds QLTM measures the core dimensions of health as defined by the Word Health Organization and school functioning in patients 2–18.[28] The age range of the study population was 5–18. When pre- and post-operative scores were compared for the CF population, SN-5 parent reported scores dropped by 1.85 ($p = .0001$). SNOT-16 parent scores declined by 10.4 ($p = .02$) and SNOT-16 child reported scores declined by 6.4 ($p = .08$). There was no significant decrease in child or parent reported PedsQLTM scores. The conclusion of this study was that there is improvement following sinus surgery in CF patients with CRS.[29]

Thamboo et al. in 2014 utilized the SNOT-22 and University of Pennsylvania Smell Identification Test (UPSIT) in an attempt to predict the presence of nasal polyposis in a group of CF patients age 6–18. Their study did not specifically evaluate the impact of disease on the SNOT-22 scores, but suggested it may be used as a tool to predict the presence of nasal polyposis in the pediatric CF population. The study found that SNOT-22 score greater than 11 had a sensitivity of 75% and specificity of 59% in the detection of nasal polyposis.[30]

More recently, Wentzel et al. evaluated a group of 50 consecutive CF patients age 2–12 that presented to a rhinology practice. The quality-of-life visual analog scale was strongly negatively correlated with reported SN-5 scores ($r = -0.55$, $p = .00006$). Additionally, worse sinus-specific QOL as measured by the SN-5 score was associated with an increase in diagnosis of sinusitis, prescription of antibiotics, and missed days of school or recreational activities due to sinonasal symptoms. No correlation was found between SN-5 score and pulmonary function or recent hospitalization. Their conclusion was that the SN-5 was a quick and qualitative method for monitoring CRS in this patient population.[8]

Finally, in a study published in 2016, Chan et al. evaluated a group of pediatric CF patients with an age range of 2–20 (average 12.9). One hundred two consecutive patients were given a screening questionnaire for diagnosis of CRS and the SN-5 during a routine clinic visit. Of the 102 participants, 47 completed the surveys. Depending on the diagnostic criteria used 11–38% of the patient population had CRS. Mean domain (2.16; 95% CI, 2.02–2.30) and overall visual-analog scale (8.26; 95% CI, 8.01–8.51) scores on the SN-5 were consistent with minimal effect on QOL. It was concluded that there is a high prevalence of symptomatic CRS in this patient population, but that it had a low impact on quality of life. [31]

DISCUSSION

Health-related QOL outcomes have become increasingly important. Patients with cystic fibrosis have a high incidence of chronic rhinosinusitis, but the impact of this disease process, on these patients' quality of life, is not well understood. Several papers have attempted to evaluate this.

The SN-5 is a questionnaire that has been validated in the non-CF patient population ages 2–12. By design, it is to be completed by the patients' proxy/primary caregiver. Several of the studies in this review use the SN-5

as part of their study design, however, only the study by Wentzel et al. used it exclusively for the 2–12 population.

In the studies by Taylor and Thamboo the SNOT-16 and SNOT-22 were used as part of the study design. However, these instruments are only validated in the >18 age group and their utility in the pediatric patient population is not well understood. Additionally, although used in multiple adult CF patient studies, the SNOT-22 has not been validated in the CF population.[32]

Several studies in the adult population have used the SNOT-22 in the CF population and have determined it to be a valuable tool. Habib et al. demonstrated that a score >21 was predictive of CRS diagnosis in a group of adult CF patients.[33] Other studies have evaluated the use of SNOT-22 for pre and postoperative symptom evaluation and have determined it to be a useful tool to follow patients over time.[32,34]

This review highlights the fact that there is a paucity of literature evaluating the quality of life affects on pediatric patients with CF associated CRS. However, the use of these instruments in the adult CF population has shown promise. Currently, no disease specific quality of life measure exists for this patient population. Although the SN-5 has shown promise, it is only validated in the non-CF 2–12 year-old patient population. This leaves no validated measurement tool for the >12 to <18 population. It is likely that the true impact of CRS on pediatric CF patients will not be known until a validated measure exists that encompasses all patients <18.

CONCLUSION

Despite the high frequency of chronic rhinosinusitis in the pediatric CF patient population, its impact on quality of life is not well understood. Currently there is a lack of a validated disease specific, quality of life instrument, available to assess the impact of CRS on the pediatric CF patient population.

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