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Chronic rhinosinusitis and endoscopic sinus surgery in children admitted for pulmonary exacerbations of cystic fibrosis

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ABSTRACT

Objective: Non-surgical management of chronic rhinosinusitis (CRS) in children with cystic fibrosis (CF) has been increasing over the last decade. This study examines inpatient children with pulmonary exacerbation of CF who were also diagnosed with CRS and underwent endoscopic sinus surgery (ESS).
Study design: We used the 2003 to 2016 Kids Inpatient Database to perform a cross-sectional analysis of inpatients (ages 0–21 years) diagnosed with CF and CRS in the United States from 2003 to 2016. Demographics and CF-associated comorbidities were recorded and rates of CRS and ESS in children with CF were examined.
Results: 49,110 children were included in the study. A total of 9334 (19%) were diagnosed with CRS. The average age was 13 (SD 5.9) years; the majority were female (56%), and White (67%). The prevalence of CRS increased from 2003 to 2016 (14%–23%, $p < 0.001$) while the rate of ESS decreased (20%–11%, $p < .001$). Patients with CRS that underwent ESS more commonly had CF-associated comorbidities including GI manifestations (15%–25%, $p < .001$) and liver disease (15%–30%, $p < .001$).
Conclusion: The diagnosis of CRS in children with CF hospitalized for pulmonary exacerbation has increased while ESS has decreased in the last decade. Patients with CRS that underwent ESS more commonly had CF-associated comorbidities. Studies to determine whether children with CF-associated comorbidities are more likely to benefit from ESS are needed.

1. Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder in the Caucasian population and is caused by mutations in the cystic fibrosis transmembrane receptor (CFTR) gene on chromosome 7. These mutations lead to defects in the CFTR protein, causing dysregulation of chloride efflux across respiratory and exocrine epithelium. Lack of chloride ion transport leads to reduced water content of secretions and thick mucus, most commonly affecting the lower airways and causing pulmonary exacerbations.

The upper airways are also affected. Nearly all CF patients will have sinonasal pathology and two-thirds will develop nasal polyposis [1–3]. The prevalence of chronic rhinosinusitis (CRS) in the CF population is four times higher than in the general population [4]. The collection of inspissated mucus obstructs sinus ostia, impairs sinonasal mucociliary clearance, and allows for bacterial overgrowth [5]. Medical therapy is the first step in treatment, including intranasal steroids, decongestants, antihistamines, saline irrigation, antibiotics, and corticosteroids [5,6]. Despite the prevalence of CRS in CF patients, indications for endoscopic sinus surgery (ESS) remains unclear in both adults and children. There are differences between pediatric subspecialists in the treatment of CRS in CF patients [7] with rates of ESS in hospitalized children ranging from 1 to 24% [8].

There is a focus on the "unified airway theory," which describes the respiratory tract (nose, sinuses, larynx, trachea, and lungs) as affected by the same inflammatory and infectious process [16]. Thus treatment of sinus disease, by medical or surgical interventions, may improve pulmonary outcomes by treating sinuses as a reservoir of bacteria implicated in lung infection. However, studies report conflicting evidence of this theory [17,18].

There is a paucity of data on CF inpatients with pulmonary exacerbations and CRS. The primary objective of this study is to describe the trends of CRS and ESS in a large inpatient cohort of children with pulmonary exacerbations of CF in the United States (US). The secondary objective is to determine factors that are associated with a higher rate of ESS during hospitalization in these children.

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2. Methods

2.1. Data source

We conducted a retrospective cross-sectional analysis of CF pediatric inpatients with pulmonary exacerbations utilizing the Healthcare Cost and Utilization Project's (HCUP) Kids Inpatient Database (KID). The KID is the largest all-payer inpatient database of pediatric admissions in US [9]. It is a complex survey that, every 3 years, samples approximately three million pediatric (age < 21 years) hospital discharges across over 4000 children's hospitals per release year. The weighted sample can estimate up to 7 million admissions. The KID is limited to inpatient admissions and does not include observational status. Each record contains demographic and clinical data, including diagnoses and procedure codes. Each admission is an independent event. The KID database does not track an individual child within a single calendar year. For years before 2016, the database uses International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. For 2016, the KID uses International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. The study included the 2003, 2006, 2009, 2012, and 2016 KID databases. The 2015 database was excluded as it contained a mixture of ICD9 and ICD 10 CM codes, making data analysis difficult. This study was approved by the UT Southwestern Medical Center Institutional Review Board as exempt status.

2.2. Study population and variables

This study included children admitted with a diagnosis of CF with pulmonary exacerbation (ICD-9-CM = 277.02, ICD-10-CM = E84.0). From this population, we identified patients diagnosed with CRS (ICD-9-CM = 4730–4739, ICD-10-CM = J320 – J329). We selected patients who underwent ESS during their admission using ICD procedure codes (ICD-9-CM = 2219–2264, ICD-10-CM = 09JY0ZZ – 09TX4ZZ).

Demographic data was extracted including age, sex, and race (white, Hispanic, black, and other). The "other" category includes native Hawaiian/Pacific Islander, Asian, American Indian/Alaska Native, and other race/multiple races. We estimated the counts and percentages for children admitted with the diagnosis of CF for pulmonary exacerbation who were also diagnosed with CRS during that admission. We further determined the number of CF patients diagnosed with CRS who had endoscopic sinus surgery during the same admission. We also examined CF-associated comorbidities using ICD-9 and ICD-10 codes reported in Appendix A. CF-associated comorbidities include CF liver disease, lung transplant, and mental health disorders. CF with GI manifestation includes intestinal manifestations and pancreatic insufficiency, and CF unspecified includes metabolic and nutritional disorders.

2.3. Statistical analysis

We used Taylor series linearization for a complex survey to determine count estimates. Descriptive statistics for continuous variables used means with standard deviations (SD) and medians with interquartile ranges (IQR). Categorical data is presented as estimated counts with percentages. To determine whether the prevalence of having CRS or ESS or a CF-associated comorbidity changed over time, we determined the percent of patients for each year and compared them to the baseline year which was 2003. For each table, we present p-values based on the predicted percent. Statistics were performed with StataCorp. 2018. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. Significance was set at $p \leq 0.01$ to account for large sample sizes and multiple comparisons.

3. Results

3.1. Demographics

From 2003 to 2016, there were 49,110 children hospitalized with a diagnosis of CF with pulmonary exacerbation (Table 1). The average age was 12.9 years (SD, 5.6), and the majority were female (N = 27,273, 56%) and White (N = 33,121, 67%). Most had a CF associated comorbidity including GI manifestations (N = 10574, 22%), CF liver disease (N = 9334, 19%), and lung transplant (N = 9784, 20%); 2.9% (N = 1443) had a mental health disorder and 1% (N = 450) had a diagnosis of CF unspecified.

A total of 9333 (19%) children hospitalized with a diagnosis of CF with pulmonary exacerbation were diagnosed with CRS and 1139 (2.3%) underwent ESS. Of the children diagnosed with CRS, the average age was 14 years (SD, 4.6), and the majority were female (N = 5518, 59%) and White (N = 6627, 82%). Most had CF-associated comorbidities (Table 1).

Of the children who underwent ESS, the average age was 13 years (SD, 4.8), and the majority were female (N = 639, 56%) and White (N = 834, 86%). Most of these children also had CF-associated comorbidities including GI manifestations (N = 288, 25%), CF unspecified (N = 206, 18%) and Liver Disease (N = 261, 23%). A total of 1.1% (N = 13) had a lung transplant, with no mental health related disorders in this group.

3.2. Trends over time

Compared to 2003, the rate of diagnosis of CRS increased between 2003 and every year studied (14% in 2003 versus 24% in 2016, $p < 0.001$). The percentage of admitted patients diagnosed with CRS who received an ESS decreased over time (20% in 2003 versus 11% in 2016, $p < 0.001$) (Table 2).

Of the children with CF admitted for pulmonary exacerbation who had CRS, the reported rate of CF liver disease increased for every year studied when compared to 2003. GI Manifestations increased for every year studied starting in 2009 when compared to 2003. CF unspecified increased in 2009 and 2012 when compared to 2003 but significantly decreased in 2016. The numbers for lung transplant were low, and none of the children had an associated mental health diagnosis (Table 3). For the children admitted for pulmonary exacerbation who underwent ESS, the rate of CF liver disease increased in 2006, 2012 and 2016 when

Table 1
Demographics of Hospitalized Children with Cystic fibrosis with Pulmonary Exacerbations, 2003–2016 Kids Inpatient Database[a,b].

	Total	CRS	ESS
N	49,110	9333 (19)	1139 (2.3)
Age, mean (SD), years	12.9 (5.6)	14.4 (4.6)	13.2 (4.8)
Female, N (%)	27,273 (56)	5518 (59)	639 (56)
White, N (%)	33,121 (78)	6627 (82)	834 (86)
Hispanic, N (%)	5210 (13)	911 (11)	72 (7.5)
Black, N (%)	1773 (4.3)	277 (3.4)	27 (2.8)
Other, N (%)	9007 (2.7)	217 (2.7)	28 (2.9)
CF GI Manifestation[c], N (%)	10574 (22)	2575 (28)	288 (25)
CF Unspecified[d], N (%)	450 (1)	1902 (20)	206 (18)
CF with Liver Disease[e], N (%)	9334 (19)	2109 (23)	261 (23)
Lung Transplant, N (%)	9784 (20)	127 (1.4)	13 (1.1)
Mental Health, N (%)	1443 (2.9)	–	–

LOS = Length of stay.
SD = standard deviation.
[a] Numbers and percentages may not add up perfectly due to rounding and statistical estimations.
[b] Race percentages exclude missing values.
[c] CF GI Manifestations includes intestinal manifestations, digestive manifestations, pancreatic insufficiency.
[d] CF Unspecified includes metabolic, endocrine, and nutritional disorders.
[e] CF with Liver Disease includes cholecystitis and portal hypertension.

Table 2
Trends in chronic rhinosinusitis (CRS) and endoscopic sinus surgery (ESS) in children hospitalized with a CF pulmonary exacerbation, 2003 to 2016, Kids Inpatient Database.

	2003	2006	2009	2012	2016
CRS, N (%)	735 (14)	1727 (16)[b]	1930 (17)[b]	2472 (22)[b]	2469 (24)[b]
ESS, N (% of patients with CRS)	145 (20)	253 (15)[a]	218 (11)[b]	259 (10)[b]	264 (11)[b]

N = number.
ESS = endoscopic sinus surgery.
P = p value between the corresponding year and 2003 as the baseline (between 2003 and 2006, 2003 and 2009, 2003 and 2012, and 2003 and 2016), based on the predicted percent.CRS = chronic rhinosinusitis.
*- P < .05.
[a] - P < .01.
[b] - P < .001.

Table 3
Trends in Children with Cystic Fibrosis (CF) Admitted for Pulmonary Exacerbation with chronic rhinosinusitis (CRS) and CF- Associated Comorbidity.

Comorbidity	Year				
	2003 N = 735	2006 N = 1724	2009 N = 1930	2012 N = 2472	2016 N = 2469
GI Manifestations[a]	125 (17)	344 (20)	450 (23)[d]	929 (38)[d]	727 (29)[d]
CF Unspecified[b]	125 (17)	344 (20)	450 (23)[d]	929 (38)[d]	53 (2.1)[d]
CF with Liver Disease[c]	66 (9.0)	283 (16)[d]	354 (18)[d]	541 (22)[d]	865 (35)[d]

N = number.
P = p value between the corresponding year and 2003 as the baseline (between 2003 and 2006, 2003 and 2009, 2003 and 2012, and 2003 and 2016), based on the predicted percent.
*- P < .05.
**- P < .01.
[a] CF GI Manifestations includes intestinal manifestations, digestive manifestations, pancreatic insufficiency.
[b] CF Unspecified includes metabolic, endocrine, and nutritional disorders.
[c] CF with Liver Disease includes cholecystitis and portal hypertension.
[d] - P < .001.

compared to 2003; the rates of GI manifestation increased in 2012 and 2016 when compared to 2003. CF unspecified increased in 2012 when compared to 2003 but significantly decreased in 2016. The numbers for lung transplant were low, and none of the children had an associated mental health diagnosis (Table 4).

4. Discussion

This study examines a large national sample of inpatient children hospitalized for pulmonary exacerbation of CF over a 14 year period. Of this population, 19% were diagnosed with CRS. This is lower than other estimates of rates of CRS in CF populations, ranging from 74 to 100% [1,3,4,10]. However, many of these studies did not differentiate between inpatients and outpatients. Furthermore, while CRS is pervasive in CF patients, it may be underreported with one study reporting 10% of children with CF with symptoms [11]. There are no clinical practice guidelines for diagnosis of CRS in CF children with a dearth of validated screening questions/measures for this population. Chan et al. showed that the SN-5 (Sinonasal-5, a validated pediatric sinonasal quality of life measurement) correlated with the presence of CRS in children with CF, but the quality-of-life impact, measured using the SN-5, was low. If sinonasal symptoms are present, they are often less severe than would be expected from endoscopy or imaging [10,12]. This could be due to the

Table 4
Trends in Children with Cystic Fibrosis (CF) Admitted for Pulmonary Exacerbation who had ESS at time of admission with CF Associated Comorbidity.

Comorbidity	Year				
	2003 N = 181	2006 N = 326	2009 N = 289	2012 N = 329	2016 N = 318
GI Manifestations[a]	27 (15)	67 (21)	65 (22)	101 (32)[e]	106 (25)[e]
CF Unspecified[b]	27 (15)	67 (21)	65 (22)	106 (32)[e]	7 (2.3)[e]
CF with Liver Disease[c]	27 (15)	81 (25)[d]	51 (18)	77 (23)[d]	96 (30)[e]

N = number.
P = p value between the corresponding year and 2003 as the baseline (between 2003 and 2006, 2003 and 2009, 2003 and 2012, and 2003 and 2016), based on the predicted percent.
*- P < .05.
[a] CF GI Manifestations includes intestinal manifestations, digestive manifestations, pancreatic insufficiency.
[b] CF Unspecified includes metabolic, endocrine, and nutritional disorders.
[c] CF with Liver Disease includes cholecystitis and portal hypertension.
[d] - P < .01.
[e] - P < .001.

natural history of CF, with children not experiencing a healthy baseline to compare their symptoms to [6,10]. Another theory is that the severity of other medical issues associated with CF mask the less severe symptoms of CRS [6,10]. Our data cannot specify if a diagnosis of CRS was reached via imaging, endoscopic exam, or clinical history.

Consistent with prior studies the children with CF in this study were predominantly white (78%) and female (56%) [13,14]. The increased likelihood of hospitalization in female CF patients is not well understood as CF is known to affect both genders equally. However, many studies have shown that female CF patients tend have a worse overall survival rate, an increased risk of diabetes, and a later age of diagnosis [14]. Socioeconomic, behavioral, and hormonal differences have been postulated as possible explanations for this disparity [14].

The first key finding of this study is the increase in the diagnosis of CRS during inpatient admissions for CF pulmonary exacerbation from 2003 to 2016. This may be due to the increased awareness of and evaluation for this disease process. Increased survival rate of patients with CF has led to a growing interest in quality of life measures in this population, which can be significantly affected by sinonasal symptoms [15]. Additionally, awareness of CRS may have also increased after several studies suggested that paranasal sinuses could be a reservoir of bacteria that could cause pulmonary exacerbations [16–18].

Our study population had a rate of ESS of 2.5%. This is consistent with data from the U.S. Cystic Fibrosis Foundation (CFF) registry database, which reports that 2–3% of children with CF have ESS each year [8,19]. The study by Virgin et al. reports a higher overall ESS rate of 17% in the Pediatric Health Information System (PHIS) database from 2008 to 2011. The PHIS (in 2015) compiled data from 42 free-standing large U.S pediatric hospitals. However, considering the high variability in rates of surgical treatment and propensity for larger hospitals with larger CF centers to have a higher rate of ESS [8], this difference with our findings may simply reflect different study populations.

The second key finding is a decrease in ESS from 2003 to 2016 during the admission for pulmonary exacerbations in children with CF. ESS is thought to improve pulmonary outcomes via the "unified airway model," but data has been mixed. Short-term improvement in lung function has been observed in children with CF undergoing ESS, but without long-term improvement [20]. In a study of adult CF patients, Ayoub et al. found no difference in outcomes between those who underwent ESS at admission or when ESS was delayed and performed after a trial of medical management [21]. Thus, there is less of an impetus for ESS for CRS during an inpatient admission for pulmonary exacerbations.

Children may thus undergo planned ESS after discharge and are not included in this study.

Another possible explanation for the decrease in ESS is that nonsurgical management options have become more effective and commonplace. These include nasal saline irrigations, topical steroids, topical antibiotics, oral antibiotics, ibuprofen, and dornase alfa [5]. A handful of studies show that nasal-administered dornase alfa may help improve symptoms of CRS, however its impact on pulmonary function remains unclear [22–24]. This is further supported by annual data from the U.S. CFF registry which shows a yearly decrease in the rate of surgery for nasal polyps from 3.9% in 2014 to 1.3 in 2019. New therapies such as Ivacaftor, which target the molecular defect in CF, shows promise in its role in treating sinus disease in children with the G551D-CFTR mutation. In a multicenter, prospective cohort study of 133 patients treated with Ivacaftor, McCormick et al. reports a significant improvement in nasal and sinus symptoms [25]. One case report describes reversal of CT findings of CF-related sinus disease as well as improvement in pulmonary function suggesting great promise for future medical management [26].

CF-associated comorbidities, specifically GI manifestations (digestive issues, pancreatic insufficiency), CF liver disease, and CF unspecified (nutritional and metabolic) increased between 2003 and 2016. It is unknown if CF-associated comorbidities are affected by CRS or if CRS outcomes are affected by these comorbidities. With improved nasal breathing children may be eating and exercising more thereby improving their nutritional status. Studies are needed to better understand how CRS plays a role in the pulmonary function of children with CF and also in GI, endocrine, liver and metabolic comorbidities. In addition, the lack of mental health diagnosis in children with CF is likely due to under-reporting or omission in coding.

The HCUP KID database offers a large national pediatric population that is a major strength of this study. However, the findings of this study must be interpreted with several limitations in mind. HCUP KID data depends on the accuracy and completeness of ICD-9-CM/ICD-10-CM coding, which may be variable across different institutions in the United States and are susceptible to coding error and bias. There may be systemic variation in the database from year to year that are not accounted for. Additionally, high variability between individual institutions has been previously demonstrated [8]. As such, this study describes general trends that apply to inpatient CF patients that are limited by the availability and quality of the data. KID does not provide data on genotype, if ESS is a primary or revision surgery or information on use of specific medical treatments such as saline irrigations, steroids, CFTR modulators or dornase alfa. Furthermore, the data is deidentified, and thus there is no way to track an individual patient course over time. Thus, some patients in this dataset may have more than one admission for pulmonary manifestations of CF that are counted as separate encounters.

Prospective randomized control studies are needed to delineate the role and best timing of ESS in children with CF and CRS. There is a need for clinical practice guidelines for surgical and medical treatment of CRS in children with CF to reduce variation in treatments across institutions and specialties. Future directions include establishing objective criteria and stratification of surgical indications for ESS in inpatient CF children. Studies looking specifically at ESS in a post-transplant population of children with CF would also be helpful in determining if it limits pulmonary pathogen colonization. In addition, outcome measures for ESS in CF patients need to be established in order to quantify the efficacy of interventions. Currently, there are no validated outcome tools for children with CF with sinus symptoms. Various questionnaires have been tested and show potential promise [12,27], but require further study.

5. Conclusion

While the likelihood of being diagnosed with CRS during an inpatient hospital admission for a CF pulmonary exacerbation has increased, the likelihood of ESS performed during hospitalization has decreased. Limited data on the benefits of sinus surgery on pulmonary function and a growing repertoire of medical treatments for sinusitis may mean sinus surgery during hospitalization for a pulmonary exacerbation is often not necessary. However, other CF-associated comorbidities may play a role in the timing of ESS for CRS. Our findings highlight the need for clinical practice guidelines in the surgical and medical treatment of CRS in pediatric patients with CF.

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None.

Declaration of competing interest

None.

Appendix A

Table 1
CF –Associated Comorbidity ICD 9 and ICD 10 codes:

CF- Associated Comorbidity	ICD 9	ICD 10
CF with GI manifestations (intestinal manifestations, digestive manifestations, pancreatic insufficiency)	277.03	E84.19
CF unspecified (metabolic, endocrine, and nutritional disorders)	277.03	E84.9
CF with liver/biliary disease (cholecystitis, portal hypertension)	277.09	E84.8
Lung transplant (status and complication, rejection, infection, failure, other)	V42.6, 996.84	Z94.2, T86.81, T86.812, T 86.811, T86.818, T86.819
Mental health disorders	300.9, V40.9	F99, F48.9

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