



# Gastroesophageal Reflux Disease and Need for Antireflux Surgery in Children with Cystic Fibrosis: A Systematic Review on Incidence, Surgical Complications, and Postoperative Outcomes

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## Abstract

**Introduction** Gastroesophageal reflux disease (GERD) is associated with accelerated decline in lung health in children with cystic fibrosis (CF). Thus, antireflux surgery (ARS) is offered to a selected CF cohort with refractory GERD, but outcomes remain poorly investigated. This study aimed to determine the incidence of GERD in children with CF and to evaluate complications and outcomes of ARS.

**Materials and Methods** A systematic literature-based search was conducted using various online databases according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The number of GERD cases in pediatric CF cohorts who underwent diagnostic investigation(s) was recorded. Data on postoperative complications and outcomes (including symptoms, lung function, and nutritional status) following ARS were analyzed.

**Results** Ten articles ( $n = 289$  patients) met the defined inclusion criteria (51% male; age range, 0.5 month–36 years). The overall incidence of GERD was 46% (range, 19–81%), derived from seven studies ( $n = 212$  patients). Four publications ( $n = 82$  patients) reported on ARS due to uncontrolled GERD. All ARSs were Nissen fundoplication (majority with gastrostomy placement). Major postoperative complications occurred in 15 (18%) patients, two required redo-ARS. Median follow-up time was 2 years (range, 3 months–6 years); 59% showed symptom improvement, and pulmonary exacerbations and decline in lung function were reduced. Nutritional status mainly improved in milder CF cases. There were no deaths related to ARS.

**Conclusion** Approximately half of pediatric CF patients have GERD. Published data for children with CF are limited and heterogeneous in terms of GERD diagnosis and outcomes following ARS. However, ARS has shown to slow the deterioration of lung function in CF.

## Keywords

- ▶ gastroesophageal reflux
- ▶ cystic fibrosis
- ▶ fundoplication
- ▶ antireflux surgery
- ▶ pediatric

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## Introduction

Gastroesophageal reflux allows the passage of gastric contents into the esophagus with or without regurgitation or vomiting.<sup>1</sup> In children with cystic fibrosis (CF), gastroesophageal reflux disease (GERD) is associated with accelerated decline in lung health with increased pulmonary exacerbations and failure to thrive.<sup>2–4</sup> GERD is more common in CF than in normal patients as a result of altered gastric emptying (GE), decreased lower esophageal sphincter (LES) pressure, increased frequency of transient LES relaxation, poorer esophageal peristalsis, and high fat due to pancreatic insufficiency.<sup>5</sup> Investigations for GERD include 24-hour pH monitoring, combined pH-impedance study, upper gastrointestinal (UGI) contrast, GE scintigraphy, and esophagogastroduodenoscopy (EGD) with biopsy. Antireflux medications are commonly used to manage GERD-related symptoms in CF patients and to control progression of disease.

In children, antireflux surgery (ARS) is generally reserved for cases with failed optimal medical therapy for GERD. Fundoplication in the pediatric age group has an overall success rate of 86% in terms of complete relief of GERD symptoms.<sup>6</sup> However, adverse outcomes, including recurrence and mortality, are frequently reported in children with severe comorbidities such as neurological impairment compared with normal cases.<sup>7</sup> Although ARS is an established treatment option for children with CF, postoperative success and complication rates remain poorly documented.

The aim of this study was to determine the incidence of GERD in pediatric cohorts with CF, and to evaluate surgical complications and postoperative outcomes of ARS based on a systematic review of the published literature.

## Materials and Methods

### Information Sources and Literature-Based Search

To identify as many scientific articles as possible of reported GERD cases in pediatric CF cohorts, a systematic literature-based search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using PubMed, EMBASE, Scopus, Web of Science, CINAHL, Centre for Reviews and Dissemination, and Cochrane Central Register of Controlled Trials.<sup>8</sup> These electronic databases were last accessed on May 15, 2020, using a combination of the following linked Medical Subject Headings and search terms: “*cystic\* fibrosis\**” OR “*mucoviscidosis\**” AND “*gastro\* esoph\* reflux\**” OR “*gastric\* acid\* reflux\**.” The search was restricted to articles published in English. In addition, reference lists of identified publications were manually searched for further studies and duplicate listed items were removed.

### Selection Criteria and Data Extraction

All identified articles were reviewed by title, keywords, and abstract by one of the authors (F.F.). Publications that did not contain original research data (e.g., editorial commentaries, letters, or reviews) and experimental animal studies were excluded. Additional exclusion criteria were case reports and CF not being the primary pathology. Only articles reporting

on pediatric CF cohorts in which GERD was investigated with established diagnostic tests (i.e., UGI contrast study, pH or pH-impedance monitoring, GE scintigraphy, EGD, and esophageal biopsy) were considered as relevant. An unblinded, systematic full-text assessment of selected publications was independently performed by two of the authors (J.N. and F.F.) and all studies not giving accurate information regarding the incidence of GERD in the respective pediatric cohorts with CF were excluded. In cases of double-published or overlapping datasets from the same institution, more recent articles or those with the larger cohort size were considered for analysis. Any discrepancies between the authors were resolved by mutual consensus.

Data from selected publications were extracted into an electronic datasheet in a standardized manner, including study characteristics (i.e., authors, publication year, geographical region, study design, and cohort size) and patient characteristics (i.e., age, gender, GERD investigation[s], treatment modality, follow-up time, and outcome measures). Primary outcome measures were severity of GERD symptoms (including those related to the gastrointestinal and airway system), pulmonary exacerbations, lung function, weight, and nutritional status. Secondary outcome measures were postoperative complications and need for redo ARS. As not all of the included articles reported on surgical complications and outcomes after ARS, each specific complication and outcome parameter were recorded as the number of patients in which that item was present divided by the total number of patients in the cohorts that presented data on that item. This enabled the calculation of incidence rates for each specific complication and outcome parameter.

### Evidence Ranking and Quality Assessment

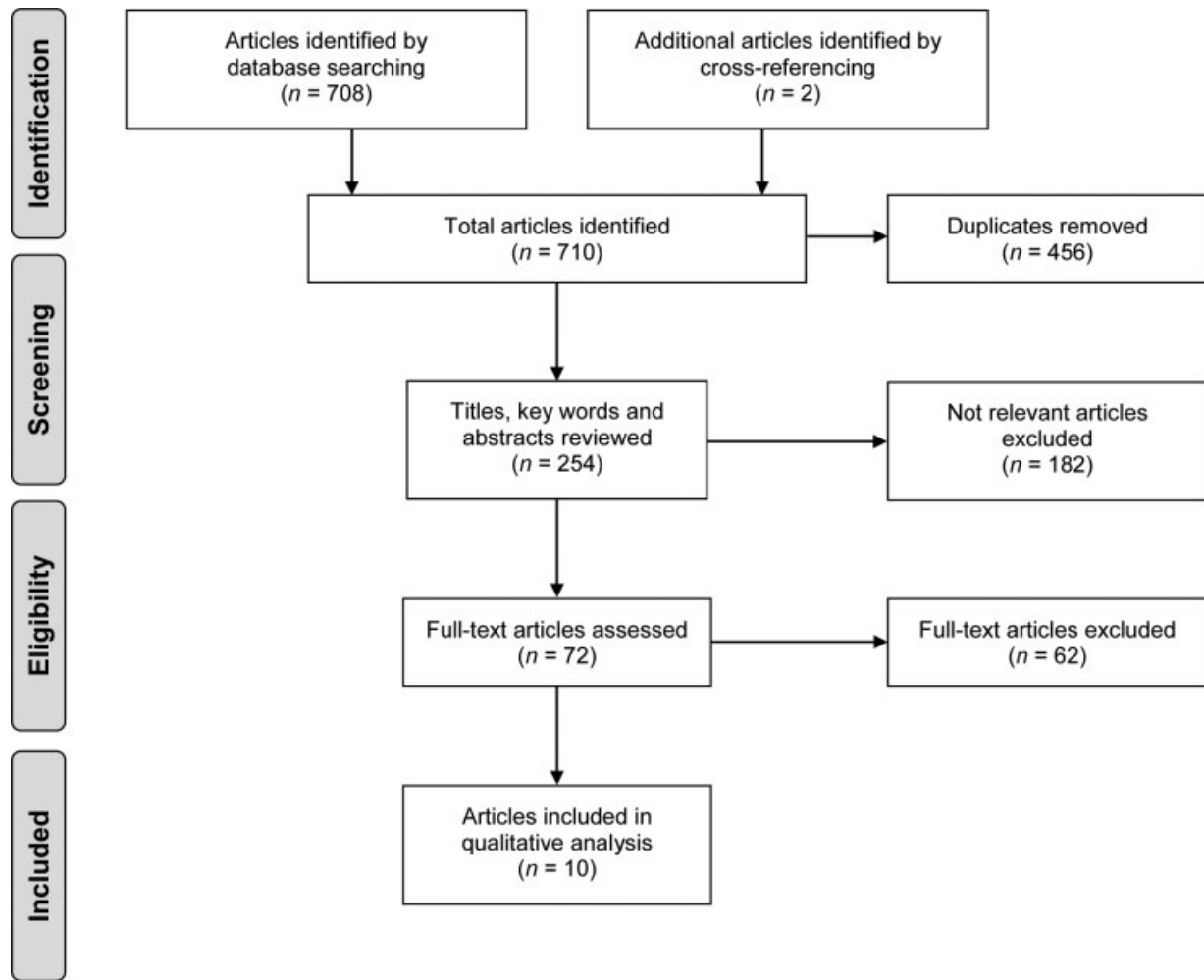
The evidence level of the included publications was ranked according to the Oxford Centre for Evidence-Based Medicine (OCEBM) classification system.<sup>9</sup> This is a hierarchical grading system, which classifies studies into Levels 1 to 5, with Level 1 representing the highest level of evidence consisting of systematic reviews of randomized controlled trials (RCTs). To reach Level 2, at least one well-designed RCT is required, whereas nonrandomized controlled cohort or follow-up studies are allocated to Level 3. Level 4 is characterized by case-control or poor-quality cohort studies, and Level 5 is assigned to mechanism-based reasoning.

The quality of selected articles was evaluated using the methodological index for nonrandomized studies (MINORS).<sup>10</sup> This validated instrument contains eight methodological items for assessment of noncomparative studies, each being scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). Thus, the ideal global score being 16.

## Results

### Literature-Based Search

The initial search yielded a total of 710 publications, of which 708 were identified by electronic database searching and 2 from cross-referencing (→ Fig. 1). After the removal of 456 duplicate listed items, 254 titles, keywords, and abstracts



**Fig. 1** Flowchart illustrating the different phases of the literature-based search and selection process.

were screened. Of these, 182 were considered as not relevant and excluded. The remaining 72 articles were assessed in full text for eligibility and 62 were excluded because they did not address all of the selection criteria. In total, data from 10 studies (published between 1982 and 2016) reporting on 289 pediatric CF patients met defined inclusion criteria and were included in the qualitative analysis.

### Overall Incidence of GERD

Seven of the 10 articles were eligible for detailed analysis of GERD incidence in pediatric CF cohorts (**Table 1**).<sup>11–17</sup> In total, there were 212 children with CF available for analysis, of which 108 (51%) were male. The median number of patients in the study cohort was 28 (range, 8–44) with an age range from 0.5 months to 20 years. Primary investigation modality for GERD and diagnostic criteria were heterogeneous, including UGI contrast study, pH, or pH-impedance monitoring. The criteria used for diagnosing GERD for pH studies differed with reflux index (RI) thresholds ranging from >1 to >10%. Diagnostic criteria for pH-impedance monitoring were RI >5 and >6%. Overall, 46% (97/212) of identified pediatric CF cases were diagnosed with GERD. The median reported GERD incidence was 50% (range, 20–81%).

### ARS-Related Complications and Postoperative Outcomes

Four of the 10 studies were eligible for detailed analysis of ARS-related outcomes and complications (**Table 2**).<sup>11,18–20</sup> A total of 82 infants and children with CF underwent ARS. The median number of CF cases in these articles was 15 (range, 4–48). Patients were aged 1 month to 36 years, of which 42 (51%) were male.

Various investigation modalities were utilized to define and assess GERD including pH monitoring ( $n = 68$  [83%]; positive result in 97%), UGI contrast study ( $n = 29$  [35%]; positive result in 48%), GE scintigraphy ( $n = 10$  [12%]; positive result in 70%), and EGD with or without biopsy ( $n = 9$  [11%]; positive result in 100%).

All ARSs were either laparoscopic or open Nissen fundoplication. The majority of patients underwent gastrostomy placement either at the same time or before ARS. The median follow-up time was 2 years (range, 3 months–6 years).

Primary outcome measures were heterogeneous across all publications and included GERD symptoms, pulmonary exacerbation episodes, rate of change in lung function (i.e., forced expiratory volume in 1 second [FEV<sub>1</sub>]), nutritional measurements (i.e., weight and/or body mass index [BMI]). Three

**Table 1** Study and patient characteristics of articles included for analysis of GERD incidence in pediatric CF cohorts

Authors	Geographical region	CF cohort (n)	Average age (range)	Selection for GERD investigation	Primary investigation modality for GERD	Investigation notes/criteria for GERD	GERD confirmed (n)	GERD incidence (%)
Vinocur et al (1985) <sup>11</sup>	Philadelphia, United States	40	Median 5 (1–24) mo	Yes, if symptomatic	UGI contrast study	-	8	20%
Gustafsson et al (1991) <sup>12</sup>	Linköping, Sweden	8	Mean 10 (4.1–14.5) y	No	pH study	RI >1%	4	50%
Malfrøot and Dab (1991) <sup>13</sup>	Brussels, Belgium	26	Median 3 (0.5–60) mo	No	pH study	Any of multiple variables <sup>a</sup> > mean + 2 SD age-matched infants	21	81%
Heine et al (1998) <sup>14</sup>	Melbourne, Australia	26	Mean 2 (0.9–5.6) mo	No	pH study	RI >10%	5	19%
Brodzicki et al (2002) <sup>15</sup>	Gdansk, Poland	40	Median 11.6 (1.3–20) y	No	pH study	RI ≥5%	22	55%
Dziewicki et al (2015) <sup>16</sup>	Warsaw, Poland	44	Mean 10.4 (3–17.8) y	No	pH-impedance study (off medications)	RI >6%	24	55%
Hauser et al (2016) <sup>17</sup>	Brussels, Belgium	28	Median 4.4 (1–17) y	No	pH-impedance study (off medications)	RI >5%	13	46%

Abbreviations: CF, cystic fibrosis; GERD, gastroesophageal reflux disease; mo, month(s); UGI, upper gastrointestinal; RI, reflux index (defined as % of time pH <4); SD, standard deviation; y, year(s).  
<sup>a</sup>Variables include: RI, duration of longest reflux episode in minutes, number of reflux episodes per hour, number of reflux episodes lasting longer than 5 minutes per hour.

studies, with a total of 34 pediatric CF patients with GERD, reported gastrointestinal symptoms following ARS.<sup>11,18,19</sup> Of these, 20 (59%) showed symptom improvement, whereas 14 (41%) had persistent or worsening of symptoms. Sheikh et al analyzed in their series 48 children with CF after fundoplication and demonstrated an average reduction of 1.3 episodes per year in pulmonary exacerbations requiring intravenous antibiotics.<sup>20</sup> They also demonstrated a significantly slowed decline in FEV<sub>1</sub> over 2 years; the mean %FEV<sub>1</sub> 2 years before ARS was 79% with a mean change by –13%, compared with a mean change of +1.5 2 years post-ARS. The nutritional status was assessed in three articles consisting of 78 pediatric CF cases that underwent fundoplication.<sup>11,19,20</sup> Overall, there was weight gain but no significant improvement in BMI. Vinocur et al's cohort of infants had gastrostomy inserted concurrently with ARS and all showed significantly increased weight and weight centiles.<sup>11</sup> The majority of Boesch and Acton's series of older children had gastrostomy concurrently with their fundoplication; however, they only found a significant increase in BMI in cases with mild lung disease (i.e., FEV<sub>1</sub> ≥60%).<sup>19</sup> Sheikh et al's patients had a significant weight gain but no improvement in BMI or BMI%.<sup>20</sup> Two-thirds of their children had gastrostomy inserted either concurrently or before ARS. It was apparent that the groups with gastrostomy supplemental feeding and those with mild lung disease demonstrated a significant weight gain.<sup>20</sup>

Major postoperative complications following fundoplication were reported in 15 (18%) patients, including loose wrap ( $n = 6$ ; 7%), paraesophageal hernia ( $n = 5$ ; 6%), perforation ( $n = 1$ ; 1%), wrap disruption ( $n = 1$ ; 1%), esophageal stricture ( $n = 1$ ; 1%), and splenic infarction ( $n = 1$ ; 1%). Two (2%) patients eventually required redo ARS. There were no deaths as a result of ARS.

### Evidence Ranking and Quality Assessment

The level of evidence of included publications was categorized in each case as OCEBM Level 4. Six were retrospective observational studies, whereas in four, the data were collected prospectively. According to the MINORS instrument, the methodological quality of these articles ranged between 7 and 12 (→ Table 3), and therefore, none of them reached the ideal global score of 16. None of the articles provided an unbiased assessment of the individual study end points or prospective calculation of the sample size.

### Discussion

GERD is prevalent in pediatric patients with CF, which may manifest in early infancy and often persists throughout childhood with deleterious effects on lung function and growth. Our systematic review revealed that 46% of children with CF have GERD. This is in comparison to a reported prevalence of 6.2% in non-CF children in a large cross-sectional observational study on more than 10,000 subjects.<sup>22</sup> Hence, all CF patients with clinical signs of GERD should be aggressively managed on an escalating pathway of medical and surgical therapies. Initially, antireflux medications control symptoms while limiting the adverse effects of GERD. The majority of medically managed

**Table 2** Study and patient characteristics of articles included for analysis of ARS-related outcomes and complications in pediatric CF cohorts

Study and patient characteristics	Bendig et al (1982) <sup>18</sup>	Vinocur et al (1985) <sup>11</sup>	Boesch and Acton (2007) <sup>19</sup>	Sheikh et al (2013) <sup>20</sup>
Geographical region	Houston, United States	Philadelphia, United States	Cincinnati, United States	Columbus, United States
CF cohort with GERD (n)	4	5	25	48
Median age (range)	14 (8–18) y	3 (1–21) mo	11 (2–16) y	14 (1–36) y
GERD investigation modality (positive result)	UGI contrast study (3/4), EGD (4/4), pH monitoring (1/1)	UGI contrast study (5/5), GE scintigraphy (4/4), EGD with biopsy (2/2)	UGI contrast study (6/20), pH monitoring (17/19), GE scintigraphy (3/6), EGD with biopsy (3/3)	pH monitoring (48/48)
GERD investigation notes	UGI contrast study (spontaneous reflux in various positions, ulceration, stricture) EGD (signs of esophagitis, stricture) pH monitoring (12–24 h, using scoring system) <sup>21</sup>	EGD (signs of esophagitis)	No details reported	24 h pH study (while on optimal dose of antireflux medications, significant acid reflux defined as RI >6%)
Type of ARS	Nissen fundoplication (open)	Nissen fundoplication (open) + gastrostomy	Nissen fundoplication (laparoscopic) ± gastrostomy	Nissen fundoplication ± gastrostomy
Gastrostomy in situ (n)	0	5 concurrent with ARS	"Majority" concurrent with ARS	4 pre-ARS, 29 concurrent with ARS
Follow-up period (range)	Unclear (3–24 mo)	Not reported	30 (6–77) mo	24 mo
<b>Postoperative outcomes</b>				
Gastrointestinal symptoms	2 (50%) asymptomatic, 2 (50%) persisted	5 (100%) no vomiting	13 (52%) better, 12 (48%) worse	Not reported
Respiratory function	-	-	1. FEV <sub>1</sub> slope 1 y pre- and post-ARS (all)—NS 2. Significant improved FEV <sub>1</sub> slope (mild lung disease) 1-y pre- and post-ARS	1. Significant reduction in pulmonary exacerbations requiring IV antibiotics 2. Significant improved FEV <sub>1</sub> at 1-y post-ARS 3. Significant slowed decline in mean %FEV <sub>1</sub> over 2 y
Nutrition	-	Significant weight and centile gain	Weight and BMI—NS	Significant weight gain, BMI—NS
<b>Postoperative complications</b>				
Perforation	-	-	1	-
Esophageal stricture	-	-	1	-
Wrap disruption	-	-	1	-
Loose wrap	-	-	-	6
Paraesophageal hernia	-	-	1	4
Splenic infarction	-	-	-	1
Redo ARS	0	0	0	2

Abbreviations: ARS, antireflux surgery; BMI, body mass index; CF, cystic fibrosis; EGD, esophagogastroduodenoscopy; FEV<sub>1</sub>, forced expiratory volume in 1 second; GE, gastric emptying; GERD, gastroesophageal reflux disease; IV, intravenous; mo, month(s); NS, not significant; RI, reflux index; UGI, upper gastrointestinal; y, year(s).

**Table 3** Quality assessment of included studies using MINORS instrument<sup>10</sup>

Methodological items for noncomparative studies <sup>a</sup>	Bendig et al (1982) <sup>18</sup>	Vinocur et al (1985) <sup>11</sup>	Gustafsson et al (1991) <sup>12</sup>	Malfrout and Dab (1991) <sup>13</sup>	Heine et al (1998) <sup>14</sup>	Brodzicki et al (2002) <sup>15</sup>	Boesch and Acton (2007) <sup>19</sup>	Sheikh et al (2013) <sup>20</sup>	Dzietkiewicz et al (2015) <sup>16</sup>	Hauser et al (2016) <sup>17</sup>
1. A clear stated aim	1	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	1	2	2	2	1	2	2	2	2	1
3. Prospective collection of data	0	0	0	2	2	0	0	0	2	2
4. End points appropriate to the aim of the study	2	1	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study end point	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	1	2	2	2	2	1	1	2	2	2
7. Loss to follow-up < 5%	2	2	2	1	2	1	1	1	2	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0
Global score <sup>b</sup>	7	9	10	11	11	8	8	9	12	11

Abbreviations: MINORS, methodological index for nonrandomized studies.

<sup>a</sup>The items were scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

<sup>b</sup>The ideal global score being 16 for noncomparative studies.

GERD is successful, but ~10% of cases fail optimal therapy with persisting GERD necessitating ARS.<sup>20</sup>

### GERD Diagnosis and Incidence in CF Children

The latest joint recommendations of the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) were published in 2018.<sup>1</sup> Both societies currently recommend that routine diagnosis for GERD is clinical in infants. In older children with typical gastrointestinal symptoms, diagnosis may be based on trial of proton pump inhibitors for 4 to 8 weeks. The use of pH or pH-impedance study, the latter being preferable, is recommended to assess efficacy of GERD treatment in high-risk patients such as those with CF. This “gold standard” was not employed in the majority of identified publications presumably due to their invasive nature. The investigations used to diagnose GERD were heterogeneous among the analyzed articles, including UGI contrast study, pH or pH-impedance monitoring, GE scintigraphy, and EGD with or without biopsy.

There are no universal “normal values” in the pediatric population, so an additional limiting factor is that studies used different criteria to diagnose GERD when using pH and pH-impedance monitoring. In three articles published between 1991 and 2002, GERD was diagnosed using pH study with varying RIs: >1, >5, >10%, or used age-matched means and standard deviations.<sup>12–15</sup> Two later articles (published in 2015 and 2016) used pH-impedance monitoring to investigate GERD and the diagnosis were based on RIs >6 and >5%, respectively.<sup>16,17</sup> However, symptom correlation for pH or pH-impedance studies was not included in their methodologies. Dziekiewicz et al specifically reported that they were unable to calculate symptom correlation parameters as patients or their parents did not note any specific symptoms.<sup>16</sup> This is not surprising as children often have poor recognition of their chronic symptoms.

In addition to the above-cited GERD investigations, children with CF often undergo computed tomography to assess for lung damage and bronchiectasis. The findings of early or deteriorating features may prompt further GERD assessment. NASPGHAN and ESPGHAN continue to recommend EGD with biopsies in patients with suspected complications of GERD prior to escalation of therapy.<sup>1</sup> Delayed GE is implicated in the pathogenesis of GERD in CF children. Although GE scintigraphy is not recommended to routinely diagnose GERD, it may be useful in children with CF when escalating to prokinetic therapies.<sup>1</sup> UGI contrast study is not recommended for routine diagnosis of GERD.<sup>1</sup> Its predominant use is to investigate whether other anatomical anomalies exist that may exacerbate symptoms of GERD or cause similar symptoms to gastroesophageal reflux which is useful prior to ARS.

### ARS-Related Outcomes and Complications

The aim of ARS in children with CF and GERD refractory to medical management is preservation of lung function to extend life expectancy and to improve their quality of life. Currently, a paucity of literature data exists on ARS in this cohort. The limited data have nonunified and subjective

outcome measures evaluating gastrointestinal symptoms, CF exacerbation, lung function (FEV<sub>1</sub>), weight, and BMI.

### Gastrointestinal Symptoms

Just more than half of the identified children with CF had symptomatic improvement in gastrointestinal symptomatology following ARS, while the remaining half had worsening or persistence of symptoms. Using symptom relief as an indicator of success of ARS in pediatric CF cases may indicate improved quality of life. However, many children with CF may have silent reflux; moreover, gastrointestinal symptom relief may not correlate with respiratory symptoms and associated lung function.

### Lung Function

The most important question the surgeon needs to answer is that by doing ARS, are we preserving pulmonary function in this cohort with refractory GERD? Data on lung function was presented in two larger studies, generally showing improved lung function.<sup>19,20</sup> Sheikh et al also demonstrated a reduction in the number of pulmonary exacerbation episodes requiring intravenous antibiotics and improved FEV<sub>1</sub> slopes 1 year after fundoplication.<sup>20</sup> Interestingly, progression of lung disease was slowed in both those with severe and mild lung diseases. Boesch and Acton compared FEV<sub>1</sub> slope of change 1 year pre- and post-ARS, and showed a significant improvement in pulmonary function only in the group with severe lung disease (i.e., FEV<sub>1</sub> <60%).<sup>19</sup>

### Nutrition Status

Severe refractory GERD affects nutrition, stunts growth, and slows development. Controlling this conversely improves nutrition in CF patients, gives fewer CF exacerbations, and reduces the rate of FEV<sub>1</sub> decline. Nutritional supplementation via gastrostomy is known to be beneficial due to increased caloric requirements of chronic disease.<sup>23</sup> The majority of pediatric CF patients in this systematic review had a gastrostomy sited at the time of or prior to their fundoplication. However, gastrostomy placement may exacerbate gastroesophageal reflux. Hence, if it is undertaken in a patient with medically managed GERD, adequate investigation (preferably with pH-impedance monitoring) and consideration ought to be given to ARS. In Vinocur et al’s study, all infants with CF who were failing to thrive prior to fundoplication had improved weight centiles following ARS with gastrostomy insertion.<sup>11</sup> Sheikh et al also showed significant weight gain in their cohort of 48 patients with CF and GERD but not in BMI 2 years after fundoplication.<sup>20</sup> The groups that exhibited weight gain were those with mild lung disease and those who received gastrostomy feeds. The majority of children in Boesch and Acton’s article had concurrent gastrostomy insertion with ARS, but the only significant improved nutritional parameter was BMI in those with mild lung disease.<sup>19</sup> Therefore, those most likely to attain nutritional benefits are infants and those with milder disease. This is probably related to supplemental feeding via gastrostomy and is evidence for early intervention to help preserve lung function.

### Postoperative Complications of ARS

Evidence suggests that the pediatric patient with CF tolerates fundoplication well. Despite being a high-risk group often requiring preoperative optimization, there were no deaths as a result of ARS. A recent systematic review of fundoplication in the children with and without neurological impairment showed poorly reported complication rates, ranging from 7 to 37%.<sup>24</sup> The present study ascertained that the ARS-related complication rate in pediatric CF patients was 18%. To note, the earlier and smaller series did not report any complications.<sup>11,18</sup> The latter two and larger series had a more comprehensive analysis of their surgical complications.<sup>19,20</sup>

### Follow-up Time

Long-term follow-up data are largely missing in this cohort of pediatric patients with CF and GERD. The majority of cases were followed up for 2 years post-ARS. The evaluation of long-term outcomes in terms of symptoms, lung function, and complications of fundoplication would help assess the efficacy and morbidity of ARS in children with CF.

### Multidisciplinary Approach and Future Study Design

Primary outcome measures in CF have altered dramatically in recent decades. With increasing life expectancy, there has been a shift in policy for lung preservation and prevention of long-term complications such as malignancy secondary to GERD. Therefore, ARS plays a crucial role in the management of these often silent aspiration events and patients must be carefully selected. Fundoplication is a prerequisite in CF patients prior to lung transplantation regardless of evidence due to the critical protection of any potential damage to the donor organ. Traditionally, pediatric patients have Nissen fundoplication performed with a complete wrap. The potential morbidity of wrap migration, failure, and gas bloat symptoms entertain the notion of jejunal feeding or partial fundoplication (e.g., anterior or posterior) to aid reflux reduction while minimizing adverse symptomatology. Jejunal feeding, in a child who would otherwise feed orally, should be the last resort or in those who pose a high risk to ARS. CF is a well-funded disease cohort in the United Kingdom with a multidisciplinary approach. Hence, it is becoming increasingly important for pediatric surgeons to be part of this team, not just for meconium ileus, distal intestinal obstruction syndrome, and venous access but also for optimal GERD management.

The primary aim of this study was to evaluate the incidence of GERD in CF and the outcomes of ARS. In order for the latter to be comprehensively concluded, future study designs must prospectively analyze this cohort, adapt an multidisciplinary approach, use standardized preoperative investigative methods (such as pH-impedance monitoring with symptom correlation scores), as well as measure unified outcome data (including the rate of decline in lung function, nutrition, and quality of life scores).

### General Limitations

CF is a rare condition and life expectancy continues to increase. Between 1987 and 1991, the median predicted

life expectancy was 29 years compared with the recent life expectancy of 44 years (2014–2018).<sup>25</sup> The studies analyzed in this review included those dating back to 1982 and we recognize CF management has changed and advanced greatly since then with significant improvement in life expectancy. Limitations of the present systematic review include the collection of heterogeneous data or limited cohort size and nonuniform outcomes. Therefore, caution must be taken when drawing firm conclusions. Two studies included several patients over the age of 18 years; however, the vast majority of patients in these larger cohorts were in the pediatric age range and thus were included to add valuable data to our review.<sup>15,20</sup>

### Conclusion

Approximately half the infants and children with CF have GERD, with around 1 in 10 of these refractory to management. While the evidence is limited, ARS has shown to slow the deterioration of lung function, and along with gastrostomy insertion, ARS can improve nutritional status in infants and children with CF. The surgeon should be part of the CF multidisciplinary team to investigate GERD and consider ARS. This can help save critical lung function and reduce cancer risk in a cohort with an ever-optimistic life expectancy.

### Conflict of Interest

None declared.

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