Cystic Fibrosis and gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux is common in children and adults with cystic fibrosis (CF). Pathological gastroesophageal reflux disease (GERD) is also frequent in patients of all ages with CF. This article reviews the pathophysiology, diagnostic work-up, management options, complications, and future directions in the evaluation and management of GERD - unique to and pertinent for - patients with CF in particular.

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1. Gastroesophageal reflux

1.1. Background

1.1.1. Definitions, clinical presentations and prevalence

Gastroesophageal reflux (GER) is the physiological phenomenon of effortless retrograde flow of gastric contents into the esophagus. GER is common in infants and young children, with symptoms occurring in ~50% of infants <3 months of age. However, GER resolves without interventions by approximately 12–14 months of age for most, and for almost all infants by about 2 years of age [1–5]. It occurs several times per day in children and adults, with the majority of reflux episodes occurring in the postprandial period, usually lasting <3 min [6–9]. In cases of persistent symptoms, they peak around the age of 16 years and reflux is more common in patients with co-morbidities such as asthma, neurological impairments and abdominal pain [1,10,11]. Feeding difficulty, regurgitation, abdominal pain are often present in young children and infants, whereas heartburn and regurgitation are more common in older children, adolescents and adults [8,9]. Symptoms of GER can be divided into typical/esophageal symptoms (such as heartburn and regurgitation) and atypical/extra-esophageal symptoms (such as chronic cough, hoarseness, wheezing and asthma) [8,9]. GER causing troublesome symptoms or complications (such as esophagitis or Barrett’s esophagus) is referred to as gastroesophageal reflux disease (GERD).

GER was first described in subjects with cystic fibrosis (CF) in 1975 by Feigelson et al. [12]. Weekly heartburn or acid regurgitation was reported in 46% of adolescent subjects with CF. In adults with CF, heartburn, acid regurgitation and dysphagia were reported on at least a weekly basis in approximately 24%, with an additional 39% experiencing symptoms occasionally [13]. Female subjects with weight loss seemed to experience more symptoms and despite the use of acid suppressive therapy, both heartburn and acid regurgitation were reported [13].

There is considerable variation in the prevalence of objectively measured GER in patients with CF, related in part to the different age groups studied as well as the different
techniques used to measure reflux in CF. The prevalence of increased esophageal acid exposure varies from 15 to 76% in infants, from 20 to 55% in children and up to 90% in adults with CF [14–25]. The gold standard to detect acid GER in the 1980’s and 1990’s was 24 h esophageal pH-monitoring. More recently, multichannel intraluminal impedance plus pH (MII-pH) monitoring was developed to detect acid reflux and non-acidic reflux episodes [26,27]. Using MII-pH, GER was detected in 67% of pediatric and 87% adult subjects with CF [20,22,28]. Acidic reflux was the most common type of GER in CF. However, there appeared to be a subgroup of pediatric and adult subjects with CF with increased weakly acidic GER [22,28]. It is important to note that not all patients with increased GER parameters experience symptoms; “silent” reflux was diagnosed in up to 60% of adult subjects with CF [21,22].

Gastroesophageal refluxate contains mostly acid and food particles. However, other components, such as pepsin, duodenal fluids with pancreatic juices and bile may also be present. Hallberg et al. demonstrated increased levels of bilirubin in the stomach of subjects with CF versus a comparison group [29]. The presence of duodeno-gastroesophageal reflux (DGER) has been detected in 35% of adult subjects with CF [20].

1.1.2. Mechanisms and pathophysiology

Several factors have been suggested to play a role in the pathophysiology of GERD including altered gastric emptying, intra-abdominal factors, anti-reflux barrier failure and intra-thoracic factors [30].

1.1.3. Gastric emptying

While there is abundant literature on gastric emptying in subjects with CF, the results are not consistent and demonstrate normal, accelerated and delayed gastric emptying [20,31,32]. While none of these studies were able to show an association between gastric emptying rate and GERD, there was a correlation between delayed gastric emptying and DGER [20].

1.1.4. Lower esophageal sphincter function

A very low basal lower esophageal sphincter (LES) pressure has been implicated as an important mechanism in GERD pathophysiology. Ledson et al. showed decreased LES pressures in a group of subjects with CF with increased GER parameters [17]. Pauwels et al. documented lower basal LES pressures in a group of adult subjects with CF versus a comparison group - albeit not pathologically low - and therefore unlikely to be a significant solitary mechanism for increased reflux in CF [33].

Transient LES relaxations (TLESRs) are relaxations of the LES not triggered by swallowing, and are the underlying mechanism for reflux of gas during belching [34,35]. TLESRs involve inhibition of the crural diaphragm, with gastric gas and meal related distention triggers; TLESRs are implicated in pediatric and adult GERD in the general population as well as in subjects with CF [19,33,34,36–39]. Although the number of TLESRs is similar in healthy subjects and in subjects with CF, they are more associated with reflux episodes. This is coincident with a higher gastro-esophageal gradient pressure (GEPG), especially during the inspiratory phase [33,40,41]. It seems that reflux in patients with CF is at least partly a secondary phenomenon to respiratory dysfunction leading to increased inspiratory effort and to lower intra-thoracic pressures [33].

1.1.5. Hiatal hernia

A hiatal hernia separates the LES from the crural diaphragm, diminishing the capacity of the gastroesophageal junction to prevent reflux. The prevalence of a hiatal hernia is approximately 17% in pediatric subjects CF and 30% of adult subjects with CF [33,42,43].

1.1.6. Peristalsis

After a reflux episode, swallow-induced or primary peristalsis affects volume clearance and helps swallowed saliva reach the distal esophagus to neutralize acid [44]. Cucchiara et al. found significantly lower amplitudes of primary peristalsis in the esophageal body in CF compared to patients with symptomatic reflux. Furthermore, the ability of primary peristalsis to clear acid from the esophageal lumen was significantly lower in subjects with CF compared to GERD patients [19]. In addition, in a study by Ledson et al., 30% of subjects with CF lacked coordinated peristalsis in the mid esophagus; abnormal peristalsis was found in 42% of subjects with CF [17,33]. These data suggest that mechanical clearance of reflux is impaired in adult subjects with CF.

Because sleeping inhibits swallowing, secondary or distention induced peristalsis may be more important during night time as a protective mechanism from refluxate [38,45]. Schoeman et al. showed that the rate of triggering secondary peristalsis in response to esophageal distention was significantly lower in patients with GERD compared to healthy subjects [46]. The same group observed that most patients with abnormal secondary peristalsis showed normal primary peristalsis, but the underlying mechanism is still unclear [46]. While direct data measurements of secondary peristalsis in CF patients is lacking, pathological nocturnal supine reflux was reported in 50% of the adult subjects with CF, suggestive of diminished secondary peristalsis in this group [20].

1.1.7. Diet and lifestyle factors

The high fat diet recommended for patients with CF and pancreatic insufficiency present in the majority of patients with CF may also exacerbate GERD [47]. Finally, we should recognize that treatment for pulmonary disease might also influence GERD. Postural drainage techniques may also increase the frequency of GER episodes in infants [48]. It has been suggested that postural drainage with the 30° head-up tilt is associated with fewer long-term GERD complications and fewer long-term respiratory complications [49,50]. Inhaled beta (2) adrenergic agonists (such as albuterol) may lower LES tone, thereby increasing risk for GERD [51,52].

2. Differential diagnosis

Symptoms of GERD vary by age, as discussed previously. The differential diagnosis for GERD includes the etiologies listed below that may present with esophagitis (below). Anatomical abnormalities can present with GERD symptoms, including hiatal
hernias, achalasia, tracheoesophageal fistulas, and pyloric stenosis in infants and younger children. Dysphagia and odynophagia may present as GERD, and may relate to underlying motility abnormalities. While GERD is often suspected in cases of epigastric pain, infectious and inflammatory gastric conditions may also present as such. Disaccharidase enzyme deficiencies or dietary fructose intolerance may present with frequent eructation and heartburn, as can small bowel bacterial overgrowth. Supra- or extraoesophageal reflux symptoms such as frequent throat clearing or nocturnal coughing may relate to airway secretions or irritation independent of GERD [7].

2.1. Diagnostic work-up

The evaluation of GER includes a comprehensive history of physical examination and assesses for clinical signs and symptoms of reflux as well as for both esophageal and extra-esophageal manifestations and potential complications of GERD. These modalities are also briefly summarized in Table 1.

### 2.1.1. Imaging

Anatomical imaging is important in the evaluation of GERD in a population at higher risk of GERD, complications related to GERD and to rule out any anatomical variants that may exacerbate GERD pathophysiology. An upper GI fluoroscopic series is used to assess esophageal and gastric anatomy, to assess for tracheoesophageal fistulae, for achalasia, hiatal hernias, and malrotation. An example of an abnormal UGI fluoroscopy series is in Figure 1. This imaging is most commonly performed in younger patients with persistent or concerning GER symptoms [7]. An UGI fluoroscopy series is an anatomical assessment. A modified barium swallow study is another type of fluoroscopy study that is used to assess swallowing function, and is often performed by radiology in conjunction with a speech and

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Table 1 Assessment tools for GERD.

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Reference values not well established across all age ranges
Not specific for GERD and aspiration of refluxate
Discordance between esophageal and laryngeal measurements of reflux monitoring
Not considered a reliable or informative test regarding supra-esophageal reflux.

Not specific for GERD and aspiration of refluxate
Not specific for GERD and aspiration of refluxate; pepsin can also be present in saliva and sputum.
language pathologist. An example of an abnormal modified barium swallow study is in Figure 2. Scintigraphy for GERD and for gastric emptying are likewise more frequently performed in pediatric patients with GERD [7]. Liquid phase studies can provide information about the proximal extent of refluxate; rarely the radiotracer can be seen in the lungs, however.

2.1.2. Endoscopy

Esophagogastroduodenoscopy (EGD)/upper endoscopy has a prominent role for the assessment of GER symptoms in patients with CF. EGD with biopsies is used to assess and characterize inflammation, if present, and to assess for additional etiologies of epigastric pain. The differential diagnosis for GERD symptoms includes anatomical abnormalities, esophagitis related to GERD eosinophilic esophagitis, esophageal candidiasis, gastritis, duodenitis, and bile reflux; celiac disease can present with epigastric pain in children [7].

Erosive esophagitis is observed with GERD. Esophagitis has been reported in at least 50% of pediatric cases of CF [15,53], and in the moderate to severe cases, esophagitis was reported in 8/10 of the pediatric subjects with CF [15]. When patients do not show lesions on upper endoscopy, they are re-classified as having non-erosive reflux disease (NERD). Eosinophilic esophagitis, NSAID related pill esophagitis, and celiac disease have been reported in subjects with CF; in the case of celiac disease, this is either detected more frequently or may truly occur at higher rates in patients with CF in these countries than that observed in the general Scandinavian population [54–56]. Both Barrett’s esophagus, a precancerous condition, as well as esophageal adenocarcinoma have been reported in patients with CF [57]. The rates of esophageal cancer at the level of gastroesophageal junction in patients with CF are higher over those observed in the general population, both in non-lung transplant and lung transplant cases [58]. Both Barrett’s esophagus and esophageal adenocarcinoma seem to occur earlier in life than reported in the general population [57–59]. Acid as well as bile exposure have been postulated in the mechanisms of development of Barrett’s esophagus [60]. An example of an endoscopic view of Barrett’s esophagus is in Figure 3. Upper endoscopy is typically performed for persistence of symptoms despite medical management, and the frequency of surveillance endoscopy follow-up likely varies across medical providers as there is not an established standard of care specifically for patients with CF.

2.1.3. Multichannel intraluminal impedance and pH testing

MII-pH testing is mainly reserved for cases of GERD refractory to dietary, and lifestyle changes as well as to acid suppressive therapy in both children and adults [7,61–63].

Fig. 1. Primary Achalasia in a 12 year old presenting with weight loss, persistent vomiting. A frontal view from a barium esophagram performed in the upright position shows a markedly dilated esophagus (arrows) with debris in the upper portion of the esophagus and a tapering of the distal esophagus at the gastroesophageal junction in a "beak-like" configuration (block arrow). This is a classic sign seen in achalasia.

Fig. 2. Frank aspiration in a 25 month old with microtia, hearing loss and difficulty swallowing. A lateral view from a modified barium swallow study performed with speech pathology shows frank aspiration (block arrow) into the trachea on the initial swallow. The barium column behind the trachea is the distended esophagus (E).
Esophageal pH monitoring, either 24 h or using a wireless capsule (Bravo® capsule) detects reflux of acidic gastric contents into the esophagus. Information about esophageal acid exposure and symptom-reflux associations can be analyzed. MII-pH detects acidic, weakly acidic and non-acidic reflux and characterizes reflux events as being liquid, gaseous, solid or mixed. Since weakly acidic and non-acid reflux episodes can provoke symptoms, MII-pH monitoring has become the gold standard in assessing GER in patients taking acid suppressive therapy. It also provides us information on the proximal extent of reflux, which might be important in the suspicion for micro-aspiration of gastric contents [64]. MII-pH provides a fuller picture missed by pH-metry alone.

2.1.4. Duodeno-gastroesophageal reflux assessment

Additional assessment considerations relate to DGER, which has been reported in adult subjects with CF [20,29]. DGER can be assessed using the Bilitec 2000 system, which measures esophageal bilirubin absorption [20].

2.1.5. Manometry

Esophageal manometry is not routinely performed in patients with CF, but can be considered in patients with dysphagia as a symptom and should strongly be considered prior to anti-reflux surgery. Manometry may help better define mechanisms of GERD, but in itself is not sufficient to diagnose GERD [7]. Using conventional manometry, Ledson et al. demonstrated that 3/10 adult subjects with CF lacked coordinated peristalsis in the mid esophagus [17]. Pauwels et al. demonstrated esophageal hypomotility by high resolution manometry in 5/12 adult subjects with CF [33].

2.1.6. Other assessment modalities

Acidification of the airway and micro-aspiration as measured by tracheal breath condensate pH monitoring (to pH <5.5) has been documented in adults with CF [65]. Interpretation of results is problematic, as the pH threshold used is higher than that set for esophageal pH monitoring [66]. While lipid laden macrophages (LLM) obtained by broncho-alveolar lavage (BAL) are often discussed as potential markers for GERD and aspiration, and while they may decrease following fundoplication [67], LLM are neither specific nor sensitive for GERD [68]. Gastric pepsin has been isolated from the trachea of pediatric patients with a variety of airway diseases, including CF, and have been associated with macroscopic changes observed on laryngobronchoscopy [69]. In an adult post lung transplant study, all subjects (including those with CF) had pepsin in their BAL fluid [70]; however, BAL pepsin did not correlate to bronchiolitis obliterans complex (BO), a histological marker of chronic allograft rejection. Pepsin (from tracheal aspirates, BAL fluid, breath condensates and saliva) has been postulated to be a more specific marker of aspiration than LLM [71–74]. However, these studies have not been able to demonstrate a clear correlation between pepsin levels and micro-aspiration. In an adult study, 56% of subjects with CF had bile in the sputum, which was significantly more than observed in the study comparison groups. Sputum bile presence in subjects with CF was inversely correlated with lung function (as measured by forced expiratory volume at 1 s (FEV1)) as compared to subjects without bile in sputum. These findings suggest that micro-aspiration of bile acids is not uncommon and detrimental to lung function in subjects with CF [75].

2.2. Complications

2.2.1. General

Failure to thrive is frequently reported in association with pediatric patients with GERD, and the effects may be bidirectional, i.e., GERD limits intake, and intake of certain potentially triggering foods as well as tube feeding may provoke GERD; the pathogenesis is not clear [76]. Acid reflux increases risk for Barrett’s esophagus and esophageal cancer, as discussed above [62,77].

2.2.2. GERD and pulmonary disease

The correlation of severity of GERD and pulmonary disease in the literature is inconsistent. In infants, pH documented reflux was not associated with radiological pulmonary changes [16]. In adolescents, there was a covariation between GERD, pulmonary disease and malnutrition [43]. There is conflicting data regarding the influence of gastric acid suppression on pulmonary function [78,79]. The interplay between GERD and lung disease is complex and may be bidirectional. Postulated mechanisms for GERD to provoke respiratory symptoms include micro-aspiration, airway inflammation and/or bronchospasm [18]. Airway acidification is associated with respiratory exacerbations in patients with asthma, CF, chronic obstructive pulmonary disease and bronchopulmonary dysplasia, as reviewed elsewhere [66]. GER reaches the proximal esophagus more often in subjects with CF compared to healthy controls, which renders them more prone to pulmonary aspiration of gastric contents [33]. Esophageal acid exposure seems to be associated with cough both in pediatric and adult subjects with CF [22,28]. While much clinical and research focus has been on the
consequences of acid reflux, and while a focus of management has been on reducing acidity of refluxate, the consequences of weakly acid, non-acidic and bile reflux are recently becoming better understood. Bile acids have been detected in the sputum of more than half of adult subjects with CF. Furthermore, subjects with CF with bile acids in sputum had significantly higher concentration of neutrophil elastase compared to those without bile acids, suggestive of airway inflammation and reflected in lower FEV\textsubscript{1} [75]. Bile acids have been demonstrated in subjects with CF to elicit specific responses to repress Hypoxia-Inducible Factor 1 signaling and subsequently down regulate IL-8 and up-regulate IL-6, modulating the immune response of airway epithelial cells [80]. pH may influence the contents of refluxate and the nature of the inflammatory response. Exposure of bronchial epithelial cells from CF patients to refluxate from subjects on proton pump inhibitor (PPI) therapy was associated with higher IL-8 concentration as compared to exposure to refluxate from subjects off PPI [81]. Furthermore, patients on PPI therapy showed higher levels of endotoxin in the gastric juice compared to subjects off of PPI [81]. Bile as a medium in the airway may also modulate respiratory pathogens and alter microbial diversity, specifically, affecting *P. aeruginosa*, *Burkholderia cepecia*, and *S. aureus*, allowing them to adapt from an acute to a chronic infection [82].

2.3. Routine management

Management of GERD encompasses diet and lifestyle changes, pharmacological approaches and surgical approaches. Diet and lifestyle measures include avoidance, restriction and/or limitation of foods associated with reflux, such as acidic foods, spicy foods, caffeine and chocolate [7,61,62]. Fatty foods may also provoke GER [47], but are difficult to limit in patients with CF, as they are integral to improve essential fatty acid deficiency, to prevent and manage fat soluble vitamin deficiency, to provide energy intake, and are associated with important health outcomes [83]. Intake of smaller, more frequent meals as recommended for reflux is probably advantageous in improving overall energy intake in patients with CF as well to meet their nutritional goals. Obesity has co-incidence with GERD and is thought to be a contributing risk factor [7,62]. Although not as prevalent as in the general population, the incidence of obesity in patients with CF may be increasing [84–86]. Avoidance of tobacco is also recommended [61,62]. Elevating the head of the bed and sleeping in the left lateral decubitus position may be beneficial.

2.3.1. Acid blockers

The rationale for the use of acid suppressive therapy was to resolve reflux-induced esophagitis and to diminish symptoms of heartburn and regurgitation. Acid suppressive therapy remains the primary pharmacological approach to the management of GERD [79]. Historically, histamine-2 receptor antagonists (H\textsubscript{2}RA) have been used. H\textsubscript{2}RAs such as ranitidine are generally well tolerated and effective for mucosal healing of peptic ulcers in children with CF [87], although higher doses than those required for the general population may be required to achieve similar efficacy [88]. However, acid suppressive therapy with PPIs has become the cornerstone of GERD management, as they are more potent compared to H\textsubscript{2}RAs [89]. The duration of therapy to achieve healing and resolution of symptoms with a PPI is ~3 months in children [90], and as such provides the rationale for the initial duration of therapy for patients with GERD symptoms. Acid suppressive therapy is also used in association with pancreatic enzyme replacement therapy (PERT). The efficacy of PERT is thought to be enhanced by reducing acidity in the duodenum; although this has not been adequately studied [87,91,92].

Patients whose GERD symptoms do not completely respond to acid suppressive therapy may have ongoing weakly acidic reflux and/or bile reflux [63,93,94]. With the advent of MII-pH, it has become clear that non-acid reflux occurs frequently, and acid suppressive therapy does not reduce non-acid GER, but may mostly change the ratio of acidic to non-acid reflux [95–97]. Calibration of acid reduction therapy with a PPI or H\textsubscript{2}RA with respect to achieving optimal endpoints for the management of acidic refluxate and for efficacy for PERT have not been established.

2.3.2. Reflux inhibitors

Baclofen (a gamma-aminobutyric acid agonist) reduces the number of TSLERs and increases LES pressure. Baclofen reduces reflux events irrespective of pH, and has been used as treatment for GERD [98,99]. However, the efficacy of baclofen for GERD management in patients with CF is unknown. While bethanechol improves esophageal body tone and LES tone [100], side effects of bronchospasm are a concern. Bethanechol has caused respiratory deterioration in infants with CF and therefore may be contraindicated [101].

2.3.3. Promotility agents

Prokinetics have been employed in the treatment of GERD in the past, however, they have neither demonstrated clear or consistent benefit in GERD nor have they been extensively studied in subjects with CF. Cisapride (a serotonin 5-HT\textsubscript{4} agonist) has been shown to increase upper GI tract motility. In a group of children with CF and proven GERD, improvement in reflux parameters occurred with the use of either cisapride alone or in combination with ranitidine therapy [15]. However, in another study, cisapride improved esophageal acid exposure in only 3/7 CF children [19]. Since cisapride use was associated with risk for prolonged cardiac QT intervals it was removed from the United States market [102]. The efficacy of cisapride, metoclopramide and domperidone has been reported in pediatric subjects with respiratory symptoms [103]. The efficacy of domperidone (a selective dopamine-2 receptor antagonist) and of metoclopramide (a dopamine-2 receptor antagonist with 5-HT\textsubscript{3} receptor antagonist and 5-HT\textsubscript{4} receptor agonist effects) in subjects with CF is unknown. Metoclopramide use increases risk for tardive dyskinesia [104].

Erythromycin (frequently as an ethyl succinate-EES) and azithromycin are macrolide antibiotics that also display promotility effects, mediated by their stimulation of motilin receptors on GI smooth muscle [105]. EES improves gastric emptying on gastric
scintigraphy in patients with CF [106,107]. However, EES is able to prolong QT interval, especially when used in combination with other medications such as certain antifungals [108]. Tachyphylaxis often limits the use of EES. Azithromycin can be used in lieu of erythromycin; it has fewer drug interactions, less incidence of QT interval prolongation, a longer half-life, and fewer GI adverse effects [105,109,110]. Azithromycin has been shown to reduce postprandial acidic reflux episodes and to clear gastric bile acid pockets in adult subjects with GERD [111]. Furthermore, azithromycin has been studied in adult subjects with CF and not only reduces GERD but also lowers bile acids concentration in BAL fluid following lung transplant [112]. Azithromycin given 3 times per week has been shown to improve FEV₁ in ~1/3 of post lung transplant patients (the majority of these by 3 months), with a decrease in neutrophil elastase levels in BAL fluid, suggesting that the mechanism of action may be a reduction in inflammation [113]. As with all antibiotics, the risk/benefit ratio should be carefully weighed; a one year study of azithromycin in subjects with CF did not demonstrate prolonged pulmonary function benefit, and drug resistant S. aureus emerged at about 6 months into the trial [114]. Monitoring for cardiac arrhythmias in patients with CF on chronic azithromycin treatment has been proposed [115].

Other promotility agents have not been extensively studied in patients with CF, and their respective efficacies, considerable side effect profiles, risk/benefit ratios, and regional availability require careful consideration.

2.3.4. Surgical management

Fundoplication has traditionally been reserved for patients with GERD symptoms who partially respond to acid suppressive therapy, as an alternative to long-term medical treatment for chronic GERD and for patients who cannot protect the airway and are at risk for aspiration of gastric contents; it is infrequently recommended in the general population [7,61,62]. Fundoplication has been associated with significant co-morbidities in the short term, including gas bloat, retching, and dumping [7]. Boesch et al. showed that 27% of pediatric subjects with CF were able to be weaned off from acid suppressive therapy post-fundoplication, but 48% developed symptoms of recurrent GERD after surgery [116]. A recent pediatric outcome study regarding fundoplication for the management of severe GERD suggested improvements in FEV₁, weight gain and a decrease in CF pulmonary exacerbations following surgery [117]. The benefits of fundoplication for the management of GERD in adults however is not consistent or clear [118].

GERD has been considered as a possible cause of chronic allograft rejection after lung transplantation, which manifests itself as a fibrotic process resulting in progressive narrowing of bronchiolar lumens and airflow obstruction-BO, which is a histological diagnosis. Bronchiolitis obliterans syndrome (BOS) is based on spirometry, and is a clinical diagnosis. BOS is not specific for BO, which is an important distinction to be made when reading the relevant literature regarding lung transplant and outcomes [119]. A case report suggests that fundoplication can reverse early allograft reduction and improve pulmonary function [120]. Other studies have suggested improved allograft survival when fundoplication was performed within 90 days after transplantation [121,122]. Early aggressive management of GER in the population with CF undergoing lung transplantation appears to reduce the risk of allograft rejection and improve lung function. While there is growing consensus towards consideration to fundoplication in relationship to lung transplantation at lung transplantation centers, the optimal timing of fundoplication needs to be prospectively studied and better defined. Interestingly, fundoplication has been shown to decrease cough in subjects with CF [123].

The approach to the assessment and management of pediatric GERD and adult GERD otherwise are currently similar to those for patients without CF, and are reviewed elsewhere [7,9,61,62].

3. Complications of GERD management

Acid blockers may increase risk for community acquired pneumonia and viral gastroenteritis in children [124], bone health and renal function issues, hypomagnesemia and other micronutrient status issues (more in adults than in children) in the general population. The potential complications of acid reduction therapy for all users are reviewed elsewhere [7,61]. While the risks of acidic reflux have been established, it is less commonly known that non-acid reflux may be deleterious as well. PPIs do not reduce reflux; instead, they mainly effect a shift from acid to non-acid reflux [90,95–97]. There is growing evidence that non-acid reflux causes symptoms, more particular in GERD patients whose symptoms do not respond to acid suppressive therapy [93,94]. Some of the deleterious effects of refluxate on esophageal tissue may relate to exposure of esophageal tissue to pancreatic and biliary secretions, and may also relate to pH [125,126]. In a rabbit model, esophageal tissue exposure to pepsin was attenuated by the presence of bile salts in an acidic environment and esophageal perfusion with weakly acidic solutions (both with as well as without bile salts) is able to impair esophageal mucosa [127]. Exposure of the esophagus to bile salts may induce DNA damage to esophageal cell lines and increase the risk for esophageal dysplasia and cancer [128,129]. Acid reflux, DGFR and bile acid exposure are postulated in the mechanisms of development of Barrett’s esophagus [60,77]. Furthermore, acid suppressive therapy has been associated with increased risk for esophageal malignancy in the general population [130–132].

Acid suppressive therapy may not only influence microbiota in the stomach, but also microbiota of the airway [79]. There is a reported association between non-acid reflux in children with CF and the presence of P. aeruginosa, which in turn may decrease lung function as measured by decline in FEV₁ [133]. Azithromycin is often utilized not only to improve upper GI tract motility, but also to reduce airway inflammation, possibly by altering airway microbiota [114].

Lung transplantation itself is associated with increased acidic GERD as measured by pH monitoring both in pediatric and adult subjects with CF. Prolonged chemical clearance of esophageal refluxate in pediatric subjects with CF as compared to pediatric controls without CF has also been reported [134,135]. A recent pediatric lung transplantation study including subjects with CF demonstrated abnormal reflux by impedance or pH testing in 67% of subjects. A subset of these subjects had gastric emptying
assessed, and 26% of them had delayed gastric emptying. In this study, neither reflux burden nor fundoplication status predicted lung transplant outcomes. However, delayed gastric emptying seemed to be associated with the development of chronic lung allograft dysfunction independent of GER [136]. Lung transplantation is known to exacerbate GERD, and higher rates of esophageal cancer are observed in patients with CF following lung transplantation [58, 135].

In a group of patients post lung transplantation, patients with CF had the highest incidence of GERD, as by pH-MII monitoring [70]. Of interest, 70% of the study subjects with BO had bile acids detected in BAL fluid as compared to 31% of stable patients who did not. Furthermore, BAL peptic or bile acid presence was not reduced by PPI use, and bile acids were associated with BO. These data may suggest that bile acid aspiration in particular may contribute significantly to the progression of CF lung disease and to findings seen in rejection.

4. Potential clinical trial end points

The logical initial endpoint is successful management of GERD symptoms. However, given the complex nature of GERD and its potential relationship with pulmonary disease, respiratory end points such as respiratory exacerbations (frequency, hospitalizations, antibiotic use, FEV1 as surrogate markers), progression of lung disease, and progression to lung transplantation in patients with CF are clinically relevant endpoints.

5. Future directions

Investigation of the safety, efficacy, consequences and complications of acid suppressive therapy for the management of GER is needed. If acid suppressive agents are to be used, their use should be calibrated better to objectively measureable outcomes with endpoints of therapy more clearly defined. If they are to be used for prolonged periods of time, we may require better safety and adverse outcome surveillance in place. This holds true for esophageal, GI and pulmonary outcomes. Esophageal motility issues in the population with CF across different life stages may need to be better understood, and the role of prokinetic medications and LES plus esophageal body tone altering medications in the management of reflux needs to be more extensively and systematically investigated. Changes in gastrointestinal and pulmonary microbiota may also relate to treatment modalities and warrant further study. Fundoplication, while associated with significant GI morbidities, may have a role in preventing allograft dysfunction post lung transplant, although this remains an area of active research and debate. Precise indications and optimal timing for this intervention need to be carefully explored.

6. Clinical practice points

• Gastroesophageal reflux is quite common in patients with CF.

• There are many tools available to assess gastroesophageal reflux disease. Endoscopy and 24 h pH/multichannel intraluminal impedance studies are most commonly performed to assess GERD.

• The relationship between GERD and extra−esophageal symptoms and findings remains complex, likely bidirectional, and controversial.

• GERD is often underdiagnosed and is over treated with acid reduction therapy, and predominantly with proton pump inhibitors in patients with CF.

• Therapeutic goals and measures for the use of acid blockers and endpoint of acid reduction therapy have not been well established. Patients risk staying on acid blockers in an open ended manner.

• While acid blockers are frequently used to manage both gastroesophageal reflux disease and to enhance effectiveness of pancreatic enzyme replacement therapy, the latter has not been clearly or consistently established.

• There are risks to the use of acid reduction medications in both short and long-term use.

• Inadequate attention has been devoted to management of refluxate.

• Anti-reflux surgery/fundoplication is often clinically reserved for patients who incompletely respond to medical management.

• The literature suggests that fundoplication may reduce the risk for bronchiolitis obliterans in lung transplant patients. There is suggestion that fundoplication performed within 90 days of lung transplantation reduces risk of graft rejection.

• Fundoplication is associated with esophageal dysmotility exacerbation and may be a risk factor for Barrett’s esophagus and esophageal cancer.

7. Summary

The interaction between GERD and airway disease in CF is complex and bidirectional. GERD symptoms are common throughout the life cycle in patients with CF, and the etiology is multifactorial. We tend to underdiagnose but over treat GERD with acid suppressive therapy with PPIs in particular. The efficacy and role of prokinetics when compared to their risk benefit profile is not known. Management should be calibrated to maximize benefit and minimize significant serious risks - both acute and chronic - to the GI tract and to the airway. Long-term surveillance by means of endoscopy with biopsies and pH/impedance-pH testing may be indicated at regular intervals that still need to be defined. Surgical interventions may have a role in the setting of a failure of medical management. The relationship between the presence of reflux and lung transplantation is even more complex, and may include elements of acid reflux, bile reflux, and impaired upper GI tract motility. Fundoplication may reduce the risk of chronic rejection in post lung transplant patients. The case for and optimal timing for fundoplication should continue to be made on a case by case basis, based on objective measures and evidence until sufficient data is published to guide clinical practice more precisely.
Conflict of interest

Authors declare no conflict of interest.

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