

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

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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]. TSLERs involve inhibition of the crural diaphragm, with gastric gas and meal related distention triggers; TSLERs 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 are 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

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