

Asthma and GERD

Scope of the Problem:

There are a number of other extra-esophageal manifestations of GERD that have been observed in children which are based on epidemiological associations. For example, Rudolph et al documented a 61% prevalence of GERD in children with persistent asthma using data from 13 Different case-series and single center studies (668 patients). The diagnosis of GERD in all of the studies reviewed were based on abnormal pH studies. Furthermore, of those children with persistent asthma and abnormal esophageal pH studies, 50% had no "typical" symptoms of GERD.

Asthma occurs in 4% - 7% of the US population, and about one-third of active asthmatics are children. Asthma affects an estimated 4.8 million children, 5% of whom have persistent asthma, defined by a symptom frequency >3 times weekly. Gastroesophageal reflux (GER) symptoms, which often result in GERD, occur daily in 7% - 20% of the United States adult population. GERD is one of the top 5 most prevalent gastrointestinal conditions in adults. GERD results in 4% of pediatric hospitalizations annually of which 27% are associated with acute or chronic respiratory complaints. Asthma and GERD are common diseases that often appear to co-exist. GERD's health care costs are over 10 billion dollars annually. Additionally, it is estimated that the cost for diagnosing and treating GERD in symptomatic asthmatics would range between 1-8 billion dollars.

The extra-esophageal manifestations of GERD fall into three primary categories: pulmonary; ear nose and throat (ENT); and "other". These extra-esophageal GERD manifestations are:

- Pulmonary
 - asthma
 - chronic cough (particularly nocturnal cough)
 - pneumonia
 - bronchiolitis/bronchitis
 - apnea
 - Apparent Life-Threatening Event (ALTE)
- ENT
 - laryngitis
 - non-infectious pharyngitis
 - laryngeal/pharyngeal ulcers
 - vocal cord granuloma or polyps
 - hoarseness
 - sinusitis
 - otitis media
- Other
 - dental erosions and halitosis
 - non-specific symptoms such as globus as well as chronic throat clearing.

GERD and asthma, two chronic conditions which often begin in childhood, could potentially improve both short and long-term health outcomes, and overall quality of life.



Pathophysiology of GERD and Asthma:

DOES GERD CAUSE ASTHMA OR DOES ASTHMA CAUSE GERD OR CAN BOTH OCCUR INDEPENDENTLY ?

GERD and asthma likely co-exist, and may be pathogenetically linked. However, it is controversial whether treatment of GERD and/or GERD symptoms improves asthma control. In addition, there are no published data on how often asthmatics are treated with acid suppression medications (e.g. proton pump inhibitors, PPIs) for GERD. However, a preliminary survey from the American Lung Association's Asthma Clinical Research Centers consortium show diverse practice patterns among clinics with about 15% of children and 20% - 30% of adults being prescribed medical treatment for GERD .

The experimental and theoretical pathophysiologic links between asthma and GERD in adults have been recently summarized by Harding and Richter. Experimental perfusion of the distal esophagus with acid induces bronchoconstriction and increased airway reactivity, responses likely mediated by stimulation of vagal reflexes. Recurrent microaspiration has been shown to directly induce airway constriction or may induce chronic inflammatory changes leading to increased airways reactivity. Alternatively, bronchoconstriction and lung over-inflation may induce gastric acid reflux. Lung over-inflation,



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a common mechanical change in asthma, further reduces intra-pleural pressure below atmospheric pressure. As a result, descent of the diaphragm with inspiration increases the thoraco-abdominal pressure gradient, a change which may promote reflux of acid from the gastric to lower esophageal regions. Beta-agonist and methylxanthine bronchodilators may decrease lower esophageal sphincter (LES) tone, but it has been difficult to demonstrate in the clinical setting whether these agents actually cause and/or worsen GERD.

What are the possible presentations for a child that has GERD-associated asthma?

A possible presentation for a child with GERD-associated asthma would be symptoms of recurrent GERD. In addition, a child may have typical GERD symptoms preceding exacerbations of asthma. More frequently however are what have been called “atypical” presentations of GERD such as nocturnal coughing, or nocturnal symptoms of asthma as the presentation of GERD-associated asthma. In addition, difficult to control asthma can be one of the more common presentations in the child with GERD-induced asthma; i.e., patient compliant with the asthma medications who continues to have exacerbations of their asthma, and/or require courses of corticosteroids.

Thus, it appears that a great number of children with asthma who have GERD, have no “typical” symptoms of GERD. A recent guideline from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) supports a link between GERD and asthma, and makes treatment recommendations for the pediatric population.

Work up and/or initiation of empiric therapy for GERD in the child with asthma should be considered in the following situations:

- Asthma exacerbations despite compliance with asthma therapy (inhaled corticosteroids, beta-agonists; reduction of environmental triggers, weight loss).
- Frequent episodes of nocturnal asthma or nocturnal cough
- Two or more courses of systemic corticosteroids per year despite maintenance asthma medication use.

The NIH Expert Panel on The Diagnosis and Management of Asthma, recommends that “...for patients with poorly controlled asthma, particularly with a nocturnal component, investigation for gastroesophageal reflux may be warranted even in the absence of suggestive symptoms”. The American Thoracic Society (ATS) workshop on severe refractory asthma, concluded that GERD “...could contribute to the severity” of asthma and recommended that all patients with severe refractory asthma undergo esophageal pH probe monitoring to evaluate for the presence of GERD”. Noticeably absent in both of these “expert panel” documents were randomized placebo controlled trial data in populations with clear case and control definitions of GERD and asthma.

What are the diagnostic tests for GERD-induced asthma before initiating empiric therapy? Which class of medications is the most effective?

The clinician should realize that at present, there is no gold standard for diagnosis of extra-esophageal GERD, and that a comprehensive history and physical exam are the most common standard of practice used to initiate empiric therapy. However, clinical trials are critically needed. If diagnostic testing is performed it should be based on a working differential diagnosis.

NASPGHAN’s clinical practice guidelines for pediatric GERD reviewed the published efficacy of antireflux pharmacotherapy in children with asthma. Despite open-label, non-controlled study designs from 4 case series (168 patients), for the most part, children treated with life-style interventions plus GERD-related pharmacotherapy had a clinical improvement or reduced dosages of bronchodilators and anti-inflammatory medications. In a recent, placebo-controlled study of lansoprazole (Prevacid®) adult patients received usual asthma care, and in addition either placebo or lansoprazole 30 mg twice daily for 24 weeks. During the trial, there were significantly fewer asthma exacerbations in the lansoprazole-treated patients than the placebo-treated patients. Furthermore, fewer exacerbations in the lansoprazole group required steroid treatment. In addition, asthma symptom scores and quality-of-life measures improved in the lansoprazole group significantly more than in the placebo group.

In a study by Khoshoo et al, 46 children with moderate and persistent asthma underwent 24 hour pH monitoring. Of those children who had abnormal pH probe results (59% of the cohort), the options of surgical intervention (i.e. fundoplication) or medical therapy (i.e. ppi plus a prokinetic) were given; 18 of the cohort with abnormal pH probes chose to receive pharmacotherapy, 9 underwent fundoplication. All of those children with abnormal pHmetry who received GERD intervention had a benefit in terms of asthma outcomes, including improvement in lung function as assessed by peak flows.

In children who continue to exhibit respiratory or other extra-esophageal symptoms after a 12 week treatment course there are several options to consider. First, it is necessary to ensure that the child has been receiving the medication properly (i.e., 30 minutes prior to eating) and not chewing the granules. Increasing the dose of PPI to twice daily (particularly if the initial treatment was once daily) or increasing the mg/kg dose are options. In addition, considering investigation by 24-hour esophageal pH monitoring while still receiving PPI therapy are reasonable management alternatives in patients who may have symptoms and have been compliant with the medication and its proper administration.

When should we consider fundoplication?

There are no comparative clinical trials which provide irrefutable evidence for surgical indications. However, the following should be considered when discussing indications for anti-reflux surgery with the child with GERD and asthma. 1) The child has a need for chronic medical therapy for GERD and asthma, and/or the child is experiencing side effects of medical therapy. 2) Children with neurological impairment with oral-pharyngeal dysfunction, and risk for aspiration or 3) if a child has a strong history of regurgitant-predominant GERD with/without oral-pharyngeal dysfunction. The keys to surgical success are increased surgeon experience and children who are complete or partial medical responders to their GERD therapy. Factors which have been suggested in surgical failure, using reoperation as the outcome are: prematurity, neurological impairment and chronic respiratory conditions. Although no multicenter studies which evaluate the outcomes of surgical management of GERD, particularly in children have been reported, single center studies demonstrated that overall reoperation rates range from 4% to 29%, with the majority of second operations occurring in the first 18 months after the initial fundoplication.

Data describing the use of anti-reflux surgery in children with asthma has been recently reported. In 6 single center retrospective reviews (i.e., case series) 285 patients were evaluated in total, and of these 85% showed clinical improvement or required reduced levels of anti-asthma medication. Moreover, a number of children improved in their pulmonary function based on incentive spirometry or evening peak flows. However, none of the studies included within the case series were randomized controlled trials.

Prognosis and Summary:

Extra-esophageal GERD in children such as asthma may be more common than previously believed. Both GERD and asthma incur significant health care burdens on U.S. children. Studies demonstrate that there is biological plausibility for GERD as the cause for a number of respiratory, head and neck diseases, in particular, asthma. Unfortunately, despite the promise of multichannel intraluminal impedance testing along with pHmetry, there is no single diagnostic evaluation for the detection of extra-esophageal GERD (e.g., asthma) in children. Based on clinical impression, thorough history and physical examination, the clinician should consider the “empiric trial test” as one of the potential optimal means of diagnosis confirmation. If strategies to determine the optimal patient for GERD intervention in the face of persistent asthma are better delineated, asthma and GERD reduction could significantly impact health care costs and patient outcomes. Multicenter studies will determine if intervention with GERD-related therapy is beneficial for the control and resolution of extra-esophageal disease, in particular childhood asthma.