Recurrent croup presentation, diagnosis, and management

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Abstract

Purpose: The lack of clinical insight into recurrent croup often leads to underdiagnosis of an upper airway lesion, and subsequently, inadequate treatment. This study examined the underlying etiology, diagnosis, treatment, and clinical outcome of patients with a history of recurrent croup identified at initial presentation. The aim was to present common diagnostic features and suggest new diagnostic and management recommendations.

Materials and methods: A retrospective chart review of 17 children diagnosed with recurrent croup. Demographic, historical, and intraoperative data as noted in clinic charts were collected. Specific collected data included age, sex, chief complaint, presenting symptoms, past medical history, previous medication history, number of emergency room visits and inpatient admissions, tests/procedures performed and corresponding findings, current treatment given, and posttreatment clinical outcome.

Results: Six (35.3\%) patients presented initially with a past medical history of gastroesophageal reflux disease. Fourteen (82.3\%) patients had positive endoscopic evidence of gastroesophageal reflux. For these 14 patients, 44 laryngopharyngeal reflux lesions were noted, with 32 (72.7\%) occurring in the subglottis. All 14 patients demonstrated various degrees of subglottic stenosis ranging from 30\% to 70\% (Cotton-Myer grade I-II). All 17 patients (100\%) demonstrated subglottic stenosis ranging from 15\% to 70\% airway narrowing.

Conclusions: History suggestive of recurrent croup requires close monitoring and expedient direct laryngoscopy/bronchoscopy for diagnosis. Long-term follow-up and antireflux treatment are necessary as well as endoscopic documentation of significant reflux resolution.

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1. Introduction

Recurrent croup is a clinical entity characterized by repeated bouts of croup-like cough that occur in a relapsing and remitting nature that worsen with the onset of upper respiratory tract infections (URIs), that persist for weeks in a relapsing and remitting nature, and that reflect an exacerbation of a localized airway process. That being said, recurrent croup is a relatively common problem in the pediatric population, with a reported incidence of 6.4\% in the infant population followed up for the first 4 years of life [1]. Despite the relatively common nature of this problem, this clinical entity is not well described and is distinct from viral croup or laryngotracheobronchitis in terms of etiology and differential diagnoses. Viral croup, typically preceded by a prodrome of URI, is an acute infection characterized by hoarseness, barking cough, various degrees of inspiratory and/or expiratory stridor, and expiratory rhonchi. These symptoms suggest involvement of the larynx, subglottis, and lower respiratory tract, respectively. Viral croup is the most common cause of upper airway obstruction among children aged between 6 months to 6 years [2]. The incidence of the infection exhibits a seasonal pattern, peaking when parainfluenza type 1, respiratory syncytial virus, and influenza activities are highest. Despite its mild and self-limited nature, this infection occasionally results in severe airway obstruction with a
reported hospitalization rate ranging from 1.3% to 2.6% [3]. Certain patients have multiple bouts of croup-like symptoms similar to viral croup, except that antecedent or concurrent URI may or may not be associated. Although recurrent croup has been characterized by a constellation of signs and symptoms, it is not a specific diagnosis in itself [4]. Indeed, recurrent croup may represent a manifestation of different underlying airway narrowing processes. Initial studies in the 1970s and 1980s suggested a correlation between recurrent croup and reactive airway disease (RAD) together with other allergic diseases [5-9]. More recent studies have shifted the focus to examining the etiologic association between recurrent croup and upper airway disease processes, such as gastroesophageal reflux (GER), subglottic stenosis (SGS), and other airway narrowing diseases [4,10-12]. The lack of insight into the underlying etiology of recurrent croup often leads to misdiagnosis or underdiagnosis of an upper airway lesion and therefore results in improper or inadequate treatment. The objective of this retrospective study was to review the underlying etiology, diagnosis, treatment, and clinical outcome of patients with a history of recurrent croup identified at initial presentation.

2. Methods

After approval from institutional review board was obtained, medical records of 17 infants and children who were referred to the otolaryngology outpatient clinic with a history of recurrent croup between January 2005 and May 2006 were reviewed. Recurrent croup was defined as 2 or more episodes of croup-like symptoms including barking cough, hoarseness, inspiratory stridor, with or without dyspnea, either confirmed medically or reported by parent. In this retrospective case series, the collected data included age, sex, chief complaint, presenting symptoms, past medical history (PMH), previous medication history, number of emergency room visits and inpatient admissions, tests/procedures performed and corresponding findings, current treatment given, and posttreatment clinical outcome.

Table 1

<table>
<thead>
<tr>
<th>Study findings</th>
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<tbody>
<tr>
<td>Average age at first visit</td>
<td>3.9 (2.5 mo-11 y)</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>13/17 (3.25:1)</td>
</tr>
<tr>
<td>% Patients having PMH of RAD</td>
<td>13/17 (76.5%)</td>
</tr>
<tr>
<td>% Patients having allergy</td>
<td>5/17 (29.4%)</td>
</tr>
<tr>
<td>% Patients having PMH of GERD</td>
<td>6/17 (35.3%)</td>
</tr>
<tr>
<td>% Patients with endoscopic evidence of GERD</td>
<td>14/17 (82.4%)</td>
</tr>
<tr>
<td>% Patients with endoscopic GER changes having positive endoscopic SGS finding</td>
<td>15/15 (100.0%)</td>
</tr>
<tr>
<td>% Patients with endoscopic confirmed dx of SGS</td>
<td>17/17 (100.0%)</td>
</tr>
<tr>
<td>% Patients with endoscopically confirmed SGS having confirmed dx of GERD</td>
<td>15/17 (88.2%)</td>
</tr>
<tr>
<td>% Patients with sx improvement after starting antireflux medications</td>
<td>13/17 (76.5%)</td>
</tr>
</tbody>
</table>

All patients underwent diagnostic direct laryngoscopy/bronchoscopy (DLB) with rigid equipment as part of a diagnostic workup of recurrent croup. Endoscopic findings of any anatomic abnormalities and pathologic changes in the airway were noted at the time of DLB. Some patients underwent follow-up DLB for clinical reassessment. In addition, 2 patients underwent esophagoscopy with biopsy. All endoscopic evaluations and grading of stenosis were performed by the senior author, who has performed over a thousand DLBs, at a university-affiliated tertiary care hospital. Endoscopic findings, considered to be suggestive of pathogenic GER, included erythema and edema of the arytenoids and posterior glottis, SGS, edematous and erythematous tracheal mucosa, blunting of the tracheal carina, esophageal strictures and signs of esophagitis, and visualized active reflux during esophagoscopy. In patients with SGS, DLB was used to assess the degree of stenosis in percentage obstruction and Cotton-Myer classification (C-M grade) by comparing the individual’s endoscope size with the age-appropriate size. Although C-M classification is the most widely used grading system of SGS, we think that the ability to grade smaller changes in SGS with percentage stenosis allows judgments on clinical improvement in a more detailed fashion.

Current treatment given for each patient was recorded, and the treatment outcome represented by resolution or improvement of recurrent croup symptoms was followed up prospectively in historical time. To reduce the confounding effect of multiple treatments, the clinical outcome following a single type of treatment was studied. Specifically, cure was defined as patients with gastroesophageal reflux disease (GERD) who achieved symptom-free status while on antireflux treatment in the absence of other medical treatments (eg, antibiotics). Detailed case descriptions of 2 selected patients were also included in this study.

3. Results

The medical records of 17 children with a history of recurrent croup-like symptoms were reviewed. The summary of findings is shown in Table 1. The studied patients consisted of 13 males and 4 females (male-to-female ratio, 3.25:1). The mean age at initial visit was 3.9 years, with a range between 2.5 months and 11 years. Of the 17 studied
patients, 13 (76.5%) had a PMH of RAD. Among them, 5 (29.4%) had a prior history of allergy or atopic disease. Of the 17 patients, 6 (35.3%) presented initially with a PMH of GERD. All patients underwent endoscopic evaluation.

Of 17 patients, 14 (82.3%) had positive endoscopic evidence of GER. All 14 patients demonstrated various degrees of SGS ranging from 30% to 70% (C-M grade I-II). Among these patients, 13 had GER-related laryngopharyngeal changes seen in DLB, and 1 had an esophagogastroduodenoscopy done by an outside physician demonstrating reflux esophagitis. The remaining 3 patients, despite the absence of endoscopic evidence of GER, were found to have SGS between 15% to 70% (C-M grade I-II), meaning 100% of our studied patients with recurrent croup demonstrated a localized narrowing in the airway. No elliptically shaped cricoid cartilage was noted in any these patients.

Of the endoscopic findings of GER-related changes, 32 (72.7%) of 44 lesions were noted at the level of the
subglottis in the form of either mucosal cobblestoning, SGS, a subglottic shelf, or carinal blunting (Table 2). All 17 patients were started on antireflux medications. Thirteen (76.5%) patients demonstrated clinical improvement as noted by shortened duration of croup-like episodes, decreased symptom severity, or the patient becoming asymptomatic. These 13 patients all had positive endoscopic evidence of laryngopharyngeal reflux-related changes.

3.1. Case 1

TM was a 3-month-old male who presented with a 2-month history of recurrent croup-like cough and inspiratory stridor. The patient’s mother noted that episodes of intermittent croup-like cough would last for 1 to 2 weeks at a time and would be exacerbated by upper respiratory tract infections. The patient had no known drug allergies and had no significant PMH. On examination, the patient was noted to have croup-like cough with inspiratory stridor. In addition, costal and subcostal retractions were noted. Remainder of physical examination was normal. Endoscopic findings at the first DLB included 50% SGS (C-M grade I), arytenoid and interarytenoid edema, carinal blunting, and mucosal cobblestoning. In the subsequent DLB after antireflux treatment, SGS was reduced to 15% to 20% (C-M grade I) with minimal GER-related mucosal changes.

3.2. Case 2

JB was a 7-year-old boy who presented with a history of a persistently intermittent croup-like cough that worsened in the presence of upper respiratory tract infections. Parents related frequent upper respiratory tract infections distributed throughout fall, winter, and spring, with 8 of 10 episodes associated with a croup-like paroxysmal cough. The patient noted the presence of an intermittent cough at least 1 to 2 times per day. Multiple visits to the emergency department averaging 1 to 2 times per month along with multiple steroid treatments were noted by the patient’s mother. The patient had no known drug allergies. Past medical history was notable for IgG immunodeficiency. Physical examination of the patient was essentially unremarkable. Endoscopic findings at the initial DLB included 40% SGS (C-M grade II), subglottic shelf, and mild arytenoid erythema and edema. Repeat examination of the patient revealed an improvement to 15% SGS (C-M grade I) on DLB in addition to symptomatic improvement as noted on clinical examination.

4. Discussion

4.1. Characterization of recurrent croup

Despite being a relatively common condition in infant and pediatric populations, recurrent croup has not been well described in previous literature in terms of its epidemiology, natural history, and etiology. Recurrent croup is commonly defined as recurring episodes (more than 2) of croup-like symptoms, such as hoarseness, inspiratory stridor, and barking cough. The age at first visit of our studied population ranged from 2.5 months to 11 years, with an average of 3.9 years. There was a strong male preponderance in our patients, which was also observed in other studies [1,5,13]. Besides the croup-like symptoms, our patients also presented with other symptoms including nasal congestion, rhinorrhea, apneic pauses, and/or intercostal retractions. Although the data suggest that recurrent croup episodes were commonly preceded by a URI challenge, some patients experienced recurrent episodes in absence of a URI prodrome or symptoms. Typically, a recurrent croup episode could last from several days to weeks. There was a seasonal variation in these patients coinciding with the peak of respiratory tract infection in the fall and winter months.

Our patients were referred by primary care physicians, general pediatricians, and pediatric subspecialists for a history of “croupy cough,” “stridor,” or “airway evaluation.” Most of our patients (76.5%) had a PMH of RAD. Nevertheless, none of the patients presented with wheezing, rhonchi, or other symptoms or signs of lower respiratory tract involvement. Atopic symptoms were only found in 5 (29.4%) of the 17 patients. Many of them were treated with maximized doses of RAD medications in an attempt to control the aforementioned symptoms. Despite aggressive medical therapy for RAD, there was no documented improvement in clinical symptoms.

Although having not been well defined, spasmodic croup is often referred as a type of afebrile croup with a sudden onset, almost always at night or during sleep, significantly associated with inspiratory stridor and respiratory distress, and usually responds well to humidification [12]. The proposed pathophysiologic mechanism is spasm of the larynx related to allergy, psychological causes, URI, and/or GERD. The disease can be recurrent and usually subsides spontaneously [12]. Sharing some common characteristics with recurrent croup, spasmodic croup may indeed represent a clinical entity that fits into the pathophysiologic model proposed later in this section.

The comparison between recurrent croup and viral croup reveals that the 2 conditions indeed represent 2 different clinical entities. First, the recurring nature distinguishes recurrent croup from viral croup, which tends not to recur within the same year unless the patient is immunocompromised or infected by a different strain of pathogen. Second, viral croup first starts as an acute infection of the nasal and pharyngeal mucosa and then extends downward along the respiratory tract to the larynx, subglottic region, trachea, and even bronchi in severe cases. The involvement of the lower respiratory tract, especially the intrathoracic segment, manifests as expiratory stridor, rhonchi, or wheezing. In contrast, recurrent croup involves mainly the upper airway and spares the lower respiratory tract in most cases, as suggested by the lack of rhonchi and wheezing in its clinical manifestation.

The 2 differences between recurrent croup and viral croup suggest that the pathogenesis of the 2 conditions is
fundamentally distinct. The recurrent nature and the lack of lower respiratory tract involvement (ie, less severe infection) indicate that recurrent croup has a lower threshold to clinically significant airway obstruction. This is reinforced by the fact that a recurrent croup episode is not always preceded by URI challenge or prodrome, meaning that minimal insult or irritation to the subglottic mucosa can make patients with recurrent croup become symptomatic. All of these observations point toward a plausible explanation that all patients with recurrent croup have a baseline airway narrowing caused by various etiologies. When challenged with URI or other airway irritating processes, the additional edematous mucosal changes further constrict the already narrowed airway, therefore causing clinically significant obstruction (Fig. 1). To adequately control and treat recurrent croup, it is essential to find the true underlying cause of the existing baseline airway narrowing in the patients.

4.2. Etiologies of the baseline airway narrowing

4.2.1. Recurrent airway disease as an etiology versus comorbidity of recurrent croup

The association between recurrent croup and RAD was frequently reported in various earlier studies [5-7,14-16]. In these studies, the reported percentages of recurrent croup patients with RAD range from 40.4% to 82%, which is in good agreement with our finding of 76.5%. Despite the significant association, prior studies have been unable to conclusively demonstrate a cause-and-effect relationship. Neither temporality nor positive dose-response relationships between RAD and recurrent croup have been demonstrated. In addition, no plausible biological mechanism can fully explain the proposed hypothesis. Finally, inconsistency in the association of recurrent croup and atopic diseases further undermines the proposed causal link between RAD and recurrent croup [7-9].

Certain findings in our study argue against the causative role of RAD in reproducing recurrent croup episodes. First, most patients remained symptomatic and continued to have recurrent croup episodes despite medically maximized therapy for RAD. Furthermore, none of the patients presented with wheezing, rhonchi, or other symptoms/signs suggestive of lower respiratory tract involvement. Finally, a high percentage of the patients (82.4%) demonstrated endoscopic findings of laryngopharyngeal reflux. Together with its documented association with RAD, GERD is likely an inducing or exacerbating factor for asthmatic symptoms, hence plausibly explaining the high incidence of RAD among recurrent croup patients.

4.2.2. Gastroesophageal reflux disease as a common finding in our studied patients

In this study, GER changes in the laryngotracheal portion of the airway were very common endoscopic findings, observed in 82.3% of our recurrent croup patients. Interestingly, in our patients with recurrent croup, GERD may have been largely undiagnosed, as suggested by the observation that only 35% of our studied patients had a past diagnosis of GERD. Several other studies document the prevalence of GERD in patients with recurrent croup. In an inpatient study of children admitted for recurrent croup (2 or more episodes), GERD, which was documented by scintiscan, esophagoscopy, pH probe, and barium swallow study, was found in 15 (47%) of 32 subjects [13]. Among 16 children with 3 or more episodes, 10 (65%) had a diagnosis of GERD. In an esophageal biopsy study, 12 (75%) of 16 children with a recurrent croup history had positive esophageal biopsy results [12]. Using a double pH probe, Contencin and Narcy [16] observed pharyngeal and esophageal reflux in 8 (100%) of 8 children with recurrent croup.

In addition to the high prevalence of GERD, the outcomes of antireflux treatment in our patients give us further insight into the relationship between GERD and recurrent croup. Among 14 patients with positive endoscopic finding of GER, 12 of them showed either improvement or resolution of recurrent croup symptoms after starting the antireflux medications. Gastroesophageal reflux disease–related mucosal changes were also improved in the patients who had posttreatment follow-up endoscopic evaluation (Fig. 2 vs 3). This observation provides suggestive evidence that GERD is either a cause or a significant contributing factor to recurrent episodes of croup.

4.2.3. Subglottic stenosis

Another striking finding in our study is that 17 (100%) of the 17 studied patients had positive endoscopic findings of various degree of SGS ranging from 30% to 70% (C-M grade I-II). Compared to other recurrent croup studies, SGS was much more common in our studied patients. Waki et al [13] noted that 8 (25%) of their 32 patients with recurrent croup demonstrated anatomical airway abnormalities including SGS and laryngomalacia. Farmer and Wohl [4] reported that 24 (45%) of their 53 pediatric patients with recurrent intermittent airway obstruction had airway narrowing such as acquired laryngotracheal stenosis, congenital cricotracheal abnormality, and subglottic hemangioma. In particular, our findings support the hypothesized pathophysiologic mechanism that all recurrent croup patients have a certain degree of baseline subglottic narrowing, which lowers their threshold to clinically significant airway obstruction and makes the patient more prone to recurrent croup episodes.

Subglottic stenosis can either be congenital or acquired. The former is less common and is usually seen in patients born with small elliptically shaped cricoid cartilage [17]. The causes of acquired SGS include traumatic intubation, infection [18-33], and GERD [21-23]. Various animal models have been used to demonstrate these etiologic causes of SGS. Using a canine model, Klainer et al [24] found complete ciliary denudation after 2 hours of intubation with a minimally occlusive low-pressure cuff.
Squire et al [19] demonstrated that rabbits with intratracheal bacterial inoculation using *Staphylococcus aureus* had narrower stenoses than those that remained noninfected. Gaynor [21] observed severe mucosal ulceration and necrosis in rabbit tracheas irrigated with synthetic gastric juice of pH 1.4 and pepsin, as compared with controls with saline, which demonstrated no significant mucosal changes. Koufman [25] reported a similar finding as well as healing delay of subglottic submucosal injuries in a canine model. Although the relative contribution of various etiologies to SGS in patients with recurrent croup remains unclear, several findings in our study may provide further insight into this particular issue.

In this study, positive endoscopic findings of laryngopharyngeal manifestation of GER were found in 14 (82.4%) of 17 patients with endoscopically confirmed SGS. This prevalence of laryngopharyngeal GER finding among SGS patients was in good agreement with previous studies. In a study of 19 patients with SGS undergoing 24-hour ambulatory pH probe testing with 3- or 4-port probes, Maronian et al [26] reported that a pH of less than 4 was recorded at the level of larynx in 12 (86%) of the 14 tested patients. Yellon et al [27] also demonstrated in a series of 36 children with SGS who underwent laryngotracheal reconstruction, that 21 (81%) of the 26 tested patients had at least 1 positive test for GERD. Although the prevalence of pathologic GERD is estimated to be only 20% and 8% in infants and children after 12 months of age, respectively, the elevated GERD prevalence in patients with SGS supports the hypothesis that GERD may play an important role in the etiology of SGS [28].

The outcome of antireflux treatment could provide further evidence on the association between GERD and SGS. Four of our studied patients underwent a second DLB follow-up after antireflux treatment. Of the 4 patients, 4 (100%) demonstrated an improvement or reduction in stenosis by a magnitude ranging from 10% to 30%. Pretreatment/Post-treatment endoscopic findings of a patient demonstrating 30% stenosis reduction are shown in Fig. 2 (70% stenosis) and Fig. 3 (40% stenosis), respectively. Similarly, Jindal et al [29] reported that 7 of 7 women with idiopathic SGS who initially failed to respond to all conservative measures and radical surgical intervention required GERD medical treatment for symptom resolution. In her study of 25 pediatric SGS patients, Halstead [23] reported that the failure rate of endoscopic repair dropped dramatically after aggressive preoperative GER treatment when compared with the historical controls and additionally noted that 35% avoided surgical intervention. Gray et al [30] also described the improvement in laryngotracheoplasty outcomes with aggressive antireflux treatment.

### 4.3 Management of recurrent croup

We are proposing a diagnostic and management algorithm for patients presenting with recurrent croup-like symptoms (Fig. 4). First, a thorough history and physical should be obtained to establish the recurrent croup status. The relevant symptoms include hoarseness, barking cough, and various degrees of inspiratory and/or expiratory stridor that recur more than 2 times. Second, presence of URI symptoms, such as fever, nasal discharge, congestion, and sore throat, should be assessed. If the patient has persistent URI symptoms more than a few days, antibiotic treatment is administered to treat the superimposed bacterial infection. The next step is assessment of potential baseline airway narrowing using DLB, which provides direct visualization of any potential narrowing and “silent” laryngopharyngeal manifestations of GER. Direct laryngoscopy/bronchoscopy should be performed when the patient is free of respiratory tract infections, which may cause airway edema that hinders the ability to detect baseline airway changes. If DLB is positive for SGS and/or laryngopharyngeal reflux findings such as erythema and edema of arytenoids and posterior glottis, edematous and erythematous tracheal mucosa, and blunting of the carina, antireflux medication together with dietary and lifestyle modifications should be started immediately to control the GER. Initial conservative management includes avoidance of food containing high amounts of fat, chocolate, peppermint, caffeine, and citrus ingredients; frequent small meals taken well before bedtime; elevation of the head of the bed; and weight loss for obese children. Initial pharmacologic treatment includes H2 blockers, such as ranitidine or cimetidine, in combination with prokinetic agents (eg, metoclopramide). We routinely prefer the use of ranitidine over cimetidine because of its higher potency, longer duration, and less frequency of adverse effects and drug interaction [31,32]. Cases refractory to the above initial pharmacologic treatment may require a proton-pump inhibitor (PPI), such as omeprazole or lansoprazole. Proton-pump inhibitors are generally safe and well-tolerated medications in both adults and children [33,34]. Given the limited data and evidence, multicenter studies are needed to investigate the safety profile of the long-term use of PPIs, particularly in pediatric populations.

Although 24-hour pH probe monitoring remains the gold standard of diagnosing GERD, endoscopic studies have been shown to demonstrate good correlation with histologic studies. In an esophageal biopsy study done by Yellon et al [12], if an erythematous or edematous posterior glottis was noted, the esophageal was positive 83% and 81% of the time, respectively. Patients should then be followed up a month after starting the antireflux medications. In patients with SGS higher than 50% to 60%, DLB should be done in 3 months to follow the progression of the condition. In cases refractory to antireflux treatment, esophagogastroduodenoscopy is recommended. Referral to gastrointestinal subspecialty and pediatric surgery for potential surgical intervention for GERD may be necessary. Patients with negative DLB findings should be observed closely for any future recurrent episodes and condition progression.
5. Conclusion

Being a relatively common pediatric condition, recurrent croup should be considered, diagnosed, and managed as a separate clinical entity from viral laryngotracheobronchitis. The 2 conditions are likely to have different pathophysiological processes as suggested by the proposed models; patients with recurrent croup often have an underlying localized upper airway narrowing and a much lower threshold for airway narrowing that predisposes patients to recurrent bouts of croup-like symptoms. Our data suggest that baseline narrowing is mainly subglottic and that lowering the threshold can lead to significant clinical airway obstruction, especially when patients are challenged by URI or airway mucosal irritation such as GER. In our study, laryngopharyngeal manifestation of GER is a very common finding in recurrent croup patients. Because of the silent nature of laryngopharyngeal GER, early diagnosis of GERD is often missed. Direct laryngoscopy/bronchoscopy is recommended as the first step in the evaluation of recurrent croup to detect any potential airway narrowing and/or evidence of laryngopharyngeal GER, which is also closely associated with SGS. Appropriate antireflux medications should be started in cases with positive GERD findings on DLB to reduce the progression of the airway narrowing or stenosis. Our study shows clinical improvement in most of the studied patients with the treatment of GERD. Future prospective studies should be done to delineate a possible causal relationship between GERD and recurrent croup.

References