Extraesophageal Reflux in Pediatric Patients With Upper Respiratory Symptoms

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Objective: To systematically review published literature describing the association between reflux and upper airway symptoms in children.


Subjects: We selected articles examining reflux in conjunction with stridor, apnea, sudden infant death syndrome, life-threatening events, and laryngomalacia. Studies that focused on lower airway symptoms or adults were excluded.

Outcome Measures: Articles were abstracted for patient factors, elements of study design, methods of reflux diagnosis, and definition of pathologic reflux.

Results: Ninety-nine articles were identified, 56 of which specifically examined reflux and upper respiratory symptoms in children. Of these, 10 compared reflux incidence in symptomatic patients and a set of predetermined control patients, while the remainder reported prevalence data only. Overall, symptomatic patients were diagnosed with reflux frequently, with a range from 27% to 100%. In studies that attempted to compare patients with controls, only 2 provided statistical comparisons of the patient groups, and none adjusted for confounding owing to study design. There was marked heterogeneity in methods used to diagnose reflux in the studies reviewed, with only 34% using dual-channel pH testing; definitions of pathologic reflux were also variable.

Conclusions: Evidence seems to support the hypothesis that reflux is associated with upper airway symptoms in children. However, the strength of this correlation and the risk of upper airway symptoms attributable to reflux are difficult to determine given the limitations of available literature. Future research studies should seek standard reflux testing methods, clear comparison groups, and more rigorous statistical methods.

Consultation for upper respiratory symptoms in children is common for the pediatric otolaryngologist. In the past, gastroesophageal reflux has been considered closely associated with stridor and other upper respiratory symptoms in children. However, to our knowledge, the evidence behind this assumption and the impact of treatment on symptoms has not been previously summarized. Although some symptoms are relatively benign and can be followed expectantly (ie, stridor from laryngomalacia without failure to thrive or significant respiratory distress), other upper airway symptoms such as respiratory distress secondary to subglottic stenosis preventing extubation in a newborn or an acute life-threatening respiratory event require more immediate investigation.

Reflux is considered a risk factor for many upper respiratory symptoms in children.1 Additionally, otitis media, chronic sinusitis, lymphoid hyperplasia, hoarseness, laryngeal edema, or nodules have all been associated with reflux.2-14 Therefore, identifying and treating coexistent reflux could improve outcomes while eliminating the need for invasive procedures in this population of children.

Laryngopharyngeal reflux is a more recently identified clinical entity. In contrast to gastroesophageal reflux, laryngopharyngeal reflux involves gastric acid reflux through the upper esophageal sphincter into the pharynx rather than across the lower esophageal sphincter.15,16 As a result, laryngopharyngeal reflux can only be diagnosed by proximal (pharyngeal) pH probe placement, a technique refined in adults in the mid-1980s, but which is still not a commonly performed diagnostic modality for children despite its proposed role as the “gold standard.”15,17,18 Any episode of laryngopharyngeal reflux in adults is believed to be pathologic,19-22 and few if any episodes of
Laryngopharyngeal reflux should be considered normal in children.25-25

Laryngopharyngeal reflux has been proposed to play a key role—at least as significant as gastroesophageal reflux—in several pediatric upper airway symptoms including subglottic stenosis and acute life-threatening respiratory events. However, studies linking reflux and upper respiratory symptoms in children are heterogeneous, representing a wide range of research designs, sample sizes, definitions of reflux, and treatment protocols. Thus, the purpose of this study was to systematically review the literature with the aim of determining the strength of the available data supporting the link between reflux and upper respiratory symptoms in children.

METHODS

We searched MEDLINE, the electronic bibliography database of the US National Library of Medicine, using the Medical Subject Heading (MeSH) terms gastroesophageal reflex, aspiration, esophagitis,peptic in combination with key title and text words including stridor, apnea, ALTE (acute life-threatening respiratory event), SIDS (sudden infant death syndrome), and laryngomalacia. To identify additional studies, we examined reference lists from published guidelines and book chapters in our topic area, as well as reference lists of our initially identified articles.1,26

We then excluded non–English-language articles, those not including an abstract, those that focused solely on lower respiratory symptoms (such as asthma), and those that studied adults only. Articles that met these criteria were then abstracted by trained reviewers (K.W.R. and A.D.A.) for key outcomes and elements of study design. Because of the recognized difficulties in quality scoring of trials, we did not score studies meeting our inclusion criteria. However, abstraction forms for each article included key elements pertaining to trial design, such as reporting of important confounders or biases, comparability of the patient groups, and methods for matching patient groups or accounting for bias. Because 24-hour dual-channel pH probe monitoring is considered the gold standard diagnostic test for reflux, we abstracted all articles for whether this test was part of outcome measurements.27-30 Finally, we also specifically abstracted articles for their definition of reflux.

Or analytic plan sought to distinguish articles that could be used to determine prevalence from articles that could allow estimation of risk for symptoms attributable to reflux. To this end, we split articles into 2 groups: (1) articles that reported prevalence of reflux within a defined subset of symptomatic patients and (2) articles that compared incidence of reflux in a symptomatic population with that in a predefined control group or those that attempted to match—via study design or statistical methods—reflux incidence in symptomatic and asymptomatic patients. Although all articles were reviewed for diagnostic modalities, this smaller subset of articles was then abstracted for elements that would allow estimation of the strength of the association between reflux and upper respiratory symptoms in children.

RESULTS

OVERVIEW

We initially identified 99 articles, 43 of which were excluded because they studied animals, enrolled adults, or focused on lower airway symptoms, yielding a core list of 56 articles that examined reflux and upper respiratory symptoms in children. We then excluded 2 studies that enrolled asymptomatic patients and reported population normative data only31,32 and 3 case series that did not report explicit entry criteria.33-35 Five additional studies were excluded because they involved treatment trials but did not include a control group from which conclusions regarding prevalence could be drawn.36-40 Finally, we excluded studies in which reflux testing was performed so inconsistently that we could not discern which patients were tested and which were not,13 that reported results that were not clearly peer reviewed,3 that enrolled patients with reflux only,12,41 that did not report objective diagnostic data,42 and that correlated periods of apnea in patients with known reflux.43 Studies in which it was unclear whether symptoms and reflux incidences overlapped were also excluded.44-46

Thus, our final group of articles reported results from patients enrolled in 35 studies published since 1979. As a group, these studies were uniformly based at academic medical centers or children’s hospitals. Of these studies, 21 (60%) were performed prospectively and 14 (40%) were performed retrospectively, most often via medical record review. Of identified studies, only 12 (34%) explicitly reported results from dual-channel pH probe testing to diagnose reflux and 21 (60%) used other pH probe tests. Of additional tests, the most common modality was laryngoscopy and bronchoscopy (n=13 [37%]), followed by barium swallow (n=10 [29%]), gastric-emptying studies (n=6 [17%]), and esophageal biopsy (n=6 [17%]).

Of the 35 studies, 9 (26%) included subjects with multiple upper airway symptoms, 13 (37%) included subjects with apnea or a history of an acute life-threatening respiratory event, and 4 (11%) included subjects with laryngomalacia. Three studies (8%) examined patients with nasal obstruction or patients presenting with stridor from croup or subglottic stenosis. Sinusitis was the presenting symptom in 2 studies (6%), and hoarseness was the presenting symptom in 1 study (3%). Twenty-five articles reported data regarding prevalence only, and 10 attempted to compare reflux incidence in symptomatic patients with that of a control group.

STUDIES REPORTING REFLUX PREVALENCE IN PATIENTS WITH UPPER AIRWAY SYMPTOMS

Twenty-five articles reported the prevalence of reflux in patients with upper airway symptoms (Table 1). These articles displayed a range of definitions of reflux, with most defining pathologic reflux as various combinations of duration of esophageal acidity and severity of acidity. However, these definitions were inconsistent and ranged from rigorous, previously validated guidelines for diagnosis of reflux47,52 to those with less apparent justification.29,45

The most common symptom examined was apnea, which was a focus of investigation in 8 (32%) of these 25 identified studies, 4 (50%) of which involved premature infants. These 4 articles reported a range between 33% and 100% in reflux prevalence in premature patients with apnea compared with a range between 25% and 100% in full-term infants with reflux. A higher reflux prevalence was noted in studies that provided results of proximal pH probe testing30,66; lower prevalence of reflux was noted in studies that performed pH probe testing of shorter duration.
or that reported distal results only. A similarly broad range in reflux prevalence was noted for other upper airway symptoms, with most articles reporting prevalence of reflux in excess of 50%.

### STUDIES COMPARING CONTROL AND SYMPTOMATIC PATIENTS

Ten articles reported prevalence of reflux in patients with upper airway symptoms and attempted to compare these patients with a control patient group (Table 2). Control groups were generally defined as asymptomatic patients or patients with symptoms not related to the upper respiratory tract. Few studies attempted any matching based on age, comorbidities (ie, prematurity), or other clinical factors, and only 2 studies reported any baseline information describing these factors in their patient groups. In addition, few studies reported any specific rationale for case finding or choice of controls. Similar to the studies reporting prevalence only, these articles used variable meth-

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<table>
<thead>
<tr>
<th>Source</th>
<th>Study Description</th>
<th>Symptom</th>
<th>Prevalence of Reflux, %</th>
<th>Reflux Definition/Study Comments</th>
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</thead>
</table>
| Andze et al., 1991 | 181 of 1153 patients referred for reflux testing. All underwent single-channel 24-h pH probe testing. | Apnea, stridor | 27-56 | • Reflux was defined by Euler-Byrne score. Lower than 15% of probe time.
| Arad-Cohen et al., 2000 | 67 patients referred after ALTE. All underwent 24-h single-channel pH probe testing. | Apnea/ALTE | 53 | • Reflux was defined as pH < 4 for > 6 s. (Borderline).
| Barrington et al., 2002 | 45 Infants < 32 wk gestation without known apnea. All underwent 12-h cardiorespirogram and pH probe. | Apnea | 33 | • No definition of meaningful reflux.
| Belmont and Grundfast, 1984 | 30 Infants referred for evaluation of stridor and laryngomalacia. All underwent barium swallow. | Laryngomalacia | 80 | • Barium swallow was the primary diagnostic modality; 4 patients also underwent 24-h single-channel pH probe.
| Beste et al., 1994 | 4 Patients with choanal atresia evaluated for reflux following surgical repair. Diagnostic tests included scintiscan in 1 and 24-h dual-channel pH probes in 3. | Choanal atresia | 100 | • Criteria for nasopharyngeal reflux included a pH < 4 associated with esophageal reflux as defined by Weiner et al.
| Bouchard et al., 1999 | 105 Patients with various upper airway symptoms referred for 20-h pH probe (channel not specified). | Stridor, recurrent otitis media, laryngitis, dysphonia | 1-61 | • Positive result for reflux was defined as pH < 4 for > 4% of the time or Euler-Byrne score > 50.
| Carr et al., 2000 | 295 Patients presenting with respiratory or feeding problems who underwent barium swallow, scintiscan, 24-h pH probe (channel not specified), or esophageal biopsy. | Stertor, stridor, apnea, hoarseness, throat clearing | 73 | • Definition of reflux was not specified.
| Carr et al., 2001 | 77 Of 155 consecutive patients who underwent DL/bronch for varied indications and who had undergone a variety of reflux tests. | Dysphonia, chronic cough, stridor | 65 | • Nonuniform testing of reflux; unclear what proportion underwent 24-h pH probe testing.
| Conley et al., 1995 | 22 Symptomatic children who had 18-24-h dual-channel pH probe performed. | Nasal obstruction, stridor, apnea | 50 (By distal probe), 94 (By proximal probe) | • Positivity was defined using criteria of Vandenplas et al.
| Giannoni et al., 1998 | 33 Of 39 patients with a new diagnosis of laryngomalacia. All underwent barium swallow or 24-h pH probe test. | Laryngomalacia | 48 (“High-grade”), 18 (“Borderline”) | • Of 17 patients with reflux at proximal probe, 12 had normal esophageal pH study findings.
| Gumpert et al., 1998 | 21 Patients with flexible laryngoscopy results suggestive of reflux. All underwent 18-24-h dual-channel pH probe testing. | Hoarseness | 62 | • Reflux was not uniformly defined; pH probe results were graded according to accepted criteria.
| Halpern et al., 1990 | 837 Patients referred for reflux testing over a 10-y period. All underwent 18-24-h pH probe testing (channel not specified). | Apnea, choking, chronic cough | 25 | • Reflux was defined using authors’ previously published method.
| Halstead, 1997 | 25 Consecutive children treated for subglottic stenosis as well as 10 from a historical cohort in whom medical therapy had failed. All patients underwent dual-channel pH probes. | Subglottic stenosis | 97 | • Although they report improvement in reflux-related symptoms after treatment, it is unclear how authors differentiated reflux-related from reflux-unrelated symptoms.

(continued)
odds to diagnose reflux, with only 3 using dual-channel pH probe testing for even a proportion of patients.

Prevalence of reflux in symptomatic groups in these articles was similar to those seen in prevalence studies, with a range between 27% and 100%. Overall, most articles suggested an excess of reflux in symptomatic patients, with 7 (70%) of 10 using statistical methods to compare symptomatic patients with controls. However, other than the articles by See et al. and Newman et al., none of these articles reported more than age and sex information regarding their patients, and none attempted to account for biases in their study design using statistical methods.

The results of our systematic review suggest that, although it is highly likely that reflux is associated with upper airway symptoms in children, the strength of this correlation is very difficult to determine. The available literature comprises studies largely derived from referral centers, most of which have substantial methodo-

### Table 1. Studies Reporting Prevalence of Reflux in Patients With Upper Airway Symptoms (cont)

<table>
<thead>
<tr>
<th>Source et al.</th>
<th>Study Description</th>
<th>Symptom</th>
<th>Prevalence of Reflux, %</th>
<th>Reflux Definition/Study Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbst et al.</td>
<td>14 Patients selected because reflux was clinically suspected. 1-h Tuttle pH probe tests were performed in 13 patients.</td>
<td>Apnea</td>
<td>100</td>
<td>Reflux was defined using number of episodes &gt;15 s, &gt;5 min, longest reflux episode, and percentage of study time with a pH &lt;4.</td>
</tr>
<tr>
<td>Marin et al.</td>
<td>75 Preterm infants; all underwent 1-h 1-channel pH probe and 12-h pneumocardiogram within the week of hospital discharge.</td>
<td>Apnea</td>
<td>63</td>
<td>Gold standard testing for reflux was not used in this study.</td>
</tr>
<tr>
<td>Matthews et al.</td>
<td>24 Patients; all underwent 24-h dual-channel pH probe testing.</td>
<td>Laryngomalacia</td>
<td>66 (Esophageal), 100 (pharyngeal)</td>
<td>Criteria for reflux included a pH &lt;4 for &gt;4 s. No mention of which patients had pH &lt;4 for more than 2.5% of monitored time.</td>
</tr>
<tr>
<td>McMurray and Holinger</td>
<td>30 Patients, 23 of whom underwent reflux testing.</td>
<td>ALTE</td>
<td>53</td>
<td>Nonuniform testing of reflux.</td>
</tr>
<tr>
<td>Paton et al.</td>
<td>24 Patients with airway symptoms and/or emesis referred for evaluation. All underwent polysomnography and single-channel pH probe.</td>
<td>Apnea</td>
<td>32-57</td>
<td>Nonstandard definition of reflux: sudden fall in pH with the end of an episode defined as a rise in pH above 4.</td>
</tr>
<tr>
<td>Phipps et al.</td>
<td>30 Consecutive patients aged 2-18 yr, in whom treatment for CT-confirmed sinusitis had failed. All underwent dual-channel pH probe testing.</td>
<td>Chronic sinusitis</td>
<td>63 With GER, 20 with nasopharyngeal reflux</td>
<td>Reflux was defined as pH &lt;4 for 4.19% of monitored time.</td>
</tr>
<tr>
<td>Stroh et al.</td>
<td>24 Patients referred for airway evaluation and rigid esophagoscopy with biopsy.</td>
<td>Stridor, apnea, chronic cough</td>
<td>54</td>
<td>Reflux was defined by pathologic findings on biopsy.</td>
</tr>
<tr>
<td>Veereman et al.</td>
<td>49 Of 130 patients underwent 24-h single-channel pH probe and sleep study.</td>
<td>ALTE immediately after eating</td>
<td>69</td>
<td>No comments were made on costs or safety of procedure for diagnosis vs pH probe.</td>
</tr>
<tr>
<td>Veereman et al.</td>
<td>116 Patients with history of vomiting (n = 54), apnea, ALTE, or choking (n = 62). All underwent dual-channel pH probe testing.</td>
<td>Apnea, choking, ALTE, stridor</td>
<td>100 Proximal, 75 distal reflux</td>
<td>Authors used their own reflux definition.</td>
</tr>
<tr>
<td>Veereman et al.</td>
<td>49 Of 130 patients underwent 24-h single-channel pH probe and sleep study.</td>
<td>ALTE immediately after eating</td>
<td>69</td>
<td>Reflux was defined as pH &lt;4 for more than 5% of study time.</td>
</tr>
<tr>
<td>Vijayaratnam et al.</td>
<td>74 Patients who underwent pH probe testing (74 single channel, 55 dual channel).</td>
<td>Subglottic stenosis</td>
<td>50 (By distal probe), 88 (by proximal probe)</td>
<td>Reflux criteria for the upper and lower probe included percentage of time with pH &lt;4.0, however, no specific cutoff was used for positivit.</td>
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<tr>
<td>Yellon et al.</td>
<td>101 Patients undergoing esophageal biopsy; all had undergone previous reflux testing.</td>
<td>Cough, apnea, sinusitis, stridor</td>
<td>63-100</td>
<td>Reflux was diagnosed by esophageal biopsy.</td>
</tr>
<tr>
<td>Zalesska-Krecicka et al.</td>
<td>100 Patients with gastrointestinal symptoms and at least 1 other respiratory symptom; all underwent dual-channel pH probe.</td>
<td>Recurring hoarseness, chronic cough, throat clearing, recurrent sore throat</td>
<td>90</td>
<td>Statistically significant excess of reflux by biopsy (all P&lt;.04) in patients with apnea (33 [75%] of 44 with GER), sinusitis (10/10, 100%), stridor (42 [63%] of 67), subglottic stenosis (23 [68%] of 34), and laryngomalacia (21 [75%] of 28).</td>
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Abbreviations: ALTE, acute life-threatening event; CT, computed tomography; DL/bronch, direct laryngoscopy and bronchoscopy; GER, gastroesophageal reflux.

*Euler-Byrne score = number of reflux episodes + (4 × number of episodes of <5 min).*
logic flaws related to inconsistent methods used for diagnosing reflux, biased patient populations, and limited statistical methods.

THE DIAGNOSIS OF REFUX

There is general agreement that the 24-hour dual-channel pH probe with 1 channel in the esophagus and 1 channel in the pharynx is the diagnostic study of choice for reflux.\(^ \text{31,78,90} \) Although reproducibility of pediatric 24-hour dual-channel pH probe results has been questioned\(^ \text{86} \) and false-negative rates up to 20% have been reported, few other testing modalities have similar discriminative power. Barium swallow, scintiscan, endoscopy with biopsy, and bronchial washings for lipid-laden macrophages have been used,\(^ \text{82,86} \) but they demonstrate sensitivities and specificities lower than dual-channel pH probe.\(^ \text{91,93} \)

Investigators have tried alternate diagnostic testing to aid diagnosis of reflux. Laryngoscopy and bronchoscopy findings—especially arytenoid edema, postglottic edema, and lingual tonsillar hypertrophy—have been demonstrated to correlate with acid exposure.\(^ \text{93,94} \) However, few data exist to correlate laryngoscopy and bronchoscopy findings with pH probe results. Esophageal biopsy is promising, but also has not been compared with dual-channel pH probe testing, nor has its safety and feasibility compared with alternate testing modalities been proven.\(^ \text{94,95} \) Also, studies using esophageal biopsy did not provide any information about pharyngeal acid exposure or laryngopharyngeal reflux.

Most studies we reviewed did not use dual-channel pH probe testing for diagnosis of reflux, and most used single-probe tests. Many studies combined results from multiple reflux tests, considering a patient to have reflux if he or she had just 1 positive diagnostic test result. Such “pooled positivity criterion” further muddies the diagnostic waters in that sequential testing may magnify the imprecision of individual tests. That is, if one orders a panel

Table 2. Studies Comparing Incidence of Reflux in Control and Symptomatic Patients

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Description</th>
<th>Symptoms</th>
<th>Findings (Control vs Symptomatic)</th>
<th>Reflux Definition/Study Comments</th>
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</thead>
<tbody>
<tr>
<td>de Ajuriaguerra et al, 1991</td>
<td>20 Consecutive premature infants, 14 of whom had apnea and 6 of whom (controls) did not. All evaluated for reflux at full term using single-channel pH probe.</td>
<td>Apnea</td>
<td>33% vs 71%; ( P ) value not provided.</td>
<td>Pathologic reflux was defined as pH &lt; 4 for 10.4% of recording time.</td>
</tr>
<tr>
<td>Bibi et al, 2001</td>
<td>116 Patients undergoing bronchoscopy. Controls (( n = 62 )) had chronic respiratory symptoms refractory to medical therapy, persistent infiltrates, or suspected foreign body. Symptomatic patients (( n = 54 )) had a history of vomiting, feeding related cough, or cough not responding to treatment. All underwent reflux testing via combination of modalities.</td>
<td>Laryngomalacia, tracheomalacia</td>
<td>37% vs 75% by pH results only; ( P ) value was not significant. 39% vs 90% when reflux tests combined; ( P &lt; .05 ).</td>
<td>Reflux was defined as pH &lt; 4 for &gt; 8% of study duration, or reflux to upper esophagus was seen on barium swallow. Reflux and laryngotracheomalacia were statistically associated (( P &lt; .05 )) only when results of reflux tests (barium swallow or pH probe) were combined. Single probe pH testing may have reduced sensitivity of their findings.</td>
</tr>
<tr>
<td>Carr et al, 2001</td>
<td>95 Children younger than 2 years undergoing adenoidectomy compared with 99 control children undergoing tympanostomy tube placement without adenoidectomy. Several studies were used for diagnosis of reflux, including pH probe.</td>
<td>Adenoid hypertrophy</td>
<td>7% vs 42%; ( P &lt; .01 ).</td>
<td>Standard definitions of reflux using barium swallow and scintiscan; pH probe test result was positive if proximal probe pH &lt; 4 for &gt; 4% of the time or distal probe pH &lt; 4 for &gt; 6% of the time.</td>
</tr>
<tr>
<td>Contencin and Narcy, 1991</td>
<td>31 Patients with chronic rhinopharyngitis and otitis media, 13 of whom had “known” reflux compared with 18 patients without rhinopharyngitis symptoms referred for ear or laryngotracheal surgery. All underwent pH probe testing with a single nasopharyngeal channel.</td>
<td>Rhinopharyngitis, otitis media</td>
<td>Pharyngeal reflux episodes with pH &lt; 6, 2.3 vs 9.2; ( P &lt; .05 ). Time with pH &lt; 6, 1.1% vs 18.7%, ( P &lt; .05 ).</td>
<td>Authors chose nasopharyngeal pH &lt; 6 as definition of reflux. Results are not reported using a positivity cutoff. “Control” group included 12 with reflux, half of whom were being treated. In symptomatic group, 13 had reflux, but authors do not comment on how many of this group were being treated. Criteria for positive pH monitoring: esophageal pH &lt; 4 for &gt; 5.2% of the time or &lt; 5 for &gt; 12% of the time; criteria for nasopharyngeal positivity pH &lt; 6 for &gt; 1% of the time. Authors state this definition is arbitrary.</td>
</tr>
<tr>
<td>Contencin and Narcy, 1992</td>
<td>8 Of 14 consecutive patients referred for recurrent group compared with 6 patients with neck infections. All underwent dual-channel 24-h pH probe.</td>
<td>Croup</td>
<td>20% vs 62% esophageal reflux; ( P &lt; .05 ). 20% vs 100% nasopharyngeal pH monitoring; ( P &lt; .05 ). Mean acid exposure 5.1% vs 7.3% (( P &lt; .001 )).</td>
<td>Reflux severity was reported as differences in mean acid exposure time. No comparisons with nonrespiratory group were provided, though differences are likely to exist.</td>
</tr>
<tr>
<td>Little et al, 1997</td>
<td>Prospective study comparing 6 groups of patients (222 total patients). Patients with laryngeal symptoms compared with randomly selected intensive care unit patients. All underwent 24-h dual-channel pH probe.</td>
<td>Hoarseness, stridor, apnea</td>
<td>( \text{Pathologic reflux was defined as pH &lt; 4 for 10.4% of recording time.} )</td>
<td>( \text{Reflex was defined as pH &lt; 4 for &gt; 8% of study duration, or reflux to upper esophagus was seen on barium swallow.} )</td>
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(continued)
of 20 tests, each of which is 95% accurate, one can expect to have at least 1 false-positive test result and an inflated prevalence estimate. In contrast, many of the tests used for reflux have sensitivities far lower than 95% for detection of pathologic reflux, raising the possibility that these studies underestimate true prevalence.

Even within the studies that used pH probe testing, we observed a moderate amount of variability in the diagnostic criteria for reflux in terms of duration and severity of acid exposure. Although individual studies generally adhered to a published definition, across studies several criteria were used, limiting our ability to directly compare results. Even when appropriate diagnostic testing is performed, not all positive results necessarily mandate treatment. Some amount of reflux, especially in premature or newborn infants, may be physiologic and not pathologic. Comparison of different age groups would then reflect the natural history of improvement with age rather than true prevalence rates of pathologic reflux.

**SHOULD CLINICIANS TREAT FIRST AND ASK QUESTIONS LATER?**

Many consider treatment for reflux a necessary first step in the management of various airway symptoms. In an uncontrolled trial, patients with choanal atresia who received reflux therapy formed less granulation tissue and needed fewer revision procedures. Another investigator found that aggressive empiric treatment of reflux in patients with subglottic stenosis led to symptomatic improvement and eliminated the need for surgical intervention. However, other studies showing no impact of reflux treatment on airway surgery for subglottic stenosis have refuted this finding.

Results from our systematic review suggest a reason for these apparently conflicting findings from clinical trials, since it is likely that an uncertain link between reflux and specific upper airway symptoms leads to uncertain clinical response. Empiric reflux treatment, especially when a low-risk approach is chosen, is likely to provide more benefit than risk as a first step. However, clinicians should be aware that little high-quality evidence exists to direct them to groups of patients who are most likely to benefit.

The studies we reviewed, although suggesting higher incidence of reflux in patients with upper airway symptoms, do not yet provide ample evidence to determine the magnitude of a causal link. Such a determination will require a study design using an appropriate control group, perhaps chosen on the basis of comorbidities or stage of...
CONCLUSIONS

Our systematic review of studies examining the association between reflux and upper airway symptoms reveals that the literature has substantial shortcomings in terms of study design, reporting of results, methods to account for bias, and standard definitions of reflux. Although reflux plays an important role in some children with upper airway symptoms, the magnitude of this risk remains unclear. Future studies addressing these shortcomings will be required to provide the evidence for clinicians faced with these often challenging patients.

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