

# 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.

**Design:** Structured MEDLINE search of English-language articles published since 1966.

**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 predeter-

mined 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.

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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.<sup>1</sup> Additionally, otitis media, chronic

sinusitis, lymphoid hyperplasia, hoarseness, laryngeal edema, or nodules have all been associated with reflux.<sup>2-14</sup> 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.<sup>15,16</sup> 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."<sup>15,17,18</sup> Any episode of laryngopharyngeal reflux in adults is believed to be pathologic,<sup>19-22</sup> and few if any episodes of

laryngopharyngeal reflux should be considered normal in children.<sup>23-25</sup>

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 reflux*, *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.<sup>1,26</sup>

We then excluded non-English-language articles, those not including an abstract, those that focused solely on lower airway 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.<sup>27-30</sup> Finally, we also specifically abstracted articles for their definition of reflux.

Our 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 only<sup>31,32</sup> and 3 case series that did not report explicit entry criteria.<sup>33-35</sup> 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.<sup>36-40</sup> 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,<sup>13</sup> that reported results that were not clearly peer reviewed,<sup>5</sup> that enrolled patients with reflux only,<sup>12,41</sup> that did not report objective diagnostic data,<sup>42</sup> and that correlated periods of apnea in patients with known reflux.<sup>43</sup> Studies in which it was unclear whether symptoms and reflux incidences overlapped were also excluded.<sup>44-46</sup>

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 reflux<sup>47,52</sup> to those with less apparent justification.<sup>55,65</sup>

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 testing<sup>29,66</sup>; lower prevalence of reflux was noted in studies that performed pH probe testing of shorter duration

**Table 1. Studies Reporting Prevalence of Reflux in Patients With Upper Airway Symptoms**

Source	Study Description	Symptom	Prevalence of Reflux, %	Reflux Definition/Study Comments
Andze et al, <sup>47</sup> 1991	181 Of 1153 patients referred for reflux testing. All underwent single-channel 20-h pH probe testing.	Apnea, stridor	27-56	<ul style="list-style-type: none"> <li>Reflux was defined by Euler-Byrne score.<sup>48*</sup></li> <li>44% Had normal pH study results, 29% moderate results, and 27% had severe reflux.</li> </ul>
Arad-Cohen et al, <sup>49</sup> 2000	67 Patients referred after ALTE. All underwent 24-h single-channel pH probe testing.	Apnea/ALTE	53	<ul style="list-style-type: none"> <li>Reflux was defined as pH &lt;4 for &gt;6 s.</li> <li>21% Had "severe" reflux; 53% overall.</li> </ul>
Barrington et al, <sup>50</sup> 2002	45 Infants <32-wk gestation without known apnea. All underwent 12-h cardiorespirogram and pH probe.	Apnea	33	<ul style="list-style-type: none"> <li>No definition of meaningful reflux.</li> <li>Only tested for reflux to mid-esophagus.</li> </ul>
Belmont and Grundfast <sup>2</sup> 1984	30 Infants referred for evaluation of stridor and laryngomalacia. All underwent barium swallow.	Laryngomalacia	80	<ul style="list-style-type: none"> <li>Barium swallow was the primary diagnostic modality; 4 patients also underwent 24-h single-channel pH probe.</li> </ul>
Beste et al, <sup>3</sup> 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	<ul style="list-style-type: none"> <li>Criteria for nasopharyngeal reflux included a pH &lt;4 associated with esophageal reflux as defined by Weiner et al.<sup>51</sup></li> </ul>
Bouchard et al, <sup>52</sup> 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	<ul style="list-style-type: none"> <li>Positive result for reflux was defined as pH &lt;4 for &gt;4% of the time or Euler-Byrne score &gt;50.<sup>48*</sup></li> </ul>
Carr et al, <sup>53</sup> 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	<ul style="list-style-type: none"> <li>Definition of reflux was not specified.</li> </ul>
Carr et al, <sup>54</sup> 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	<ul style="list-style-type: none"> <li>Nonuniform testing of reflux; unclear what proportion underwent 24-h pH probe testing.</li> </ul>
Conley et al, <sup>29</sup> 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)	<ul style="list-style-type: none"> <li>Positivity was defined using criteria of Vandenplas et al.<sup>31</sup></li> <li>Of 17 patients with reflux at proximal probe, 13 had normal esophageal pH study findings.</li> </ul>
Giannoni et al, <sup>55</sup> 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")	<ul style="list-style-type: none"> <li>Reflux was not uniformly defined; pH probe results were graded according to accepted criteria.</li> </ul>
Gumpert et al, <sup>8</sup> 1998	21 Patients with flexible laryngoscopy results suggestive of reflux. All underwent 18-24-h dual-channel pH probe testing.	Hoarseness	62	<ul style="list-style-type: none"> <li>Reflux was defined as pH &lt;4 for &gt;5% of monitored time.</li> </ul>
Halpern et al, <sup>56</sup> 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	<ul style="list-style-type: none"> <li>Reflux was defined using authors' previously published method.<sup>57-59</sup></li> <li>Although they report improvement in reflux-related symptoms after treatment, it is unclear how authors differentiated reflux-related from reflux-unrelated symptoms.</li> </ul>
Halstead, <sup>9</sup> 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	<ul style="list-style-type: none"> <li>Reflux criteria included 15% of probe time with pH &lt;4, reflux episodes of &gt;5 min duration, or &gt;2 episodes of reflux per hour of probe time. No criteria were given for upper probe positivity.</li> </ul>

(continued)

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<sup>74,78</sup> 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-

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

Source	Study Description	Symptom	Prevalence of Reflux, %	Reflux Definition/Study Comments
Herbst et al, <sup>10</sup> 1979	14 Patients selected because reflux was clinically suspected. 1-h Tuttle pH probe tests were performed in 13 patients.	Apnea	100	<ul style="list-style-type: none"> <li>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.</li> </ul>
Marino et al, <sup>60</sup> 1995	75 Preterm infants; all underwent 1-h 1-channel pH probe and 12-h pneumocardiogram within the week of hospital discharge.	Apnea	63	<ul style="list-style-type: none"> <li>Gold standard testing for reflux was not used in this study.</li> <li>Did not distinguish between central and obstructive apneic episodes.</li> </ul>
Matthews et al, <sup>61</sup> 1999	24 Patients; all underwent 24-h dual-channel pH probe testing.	Laryngomalacia	66 (Esophageal), 100 (pharyngeal)	<ul style="list-style-type: none"> <li>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.</li> </ul>
McMurray and Holinger, <sup>62</sup> 1997	30 Patients, 23 of whom underwent reflux testing.	ALTE	53	<ul style="list-style-type: none"> <li>Nonuniform testing of reflux.</li> </ul>
Paton et al, <sup>63</sup> 1990	24 Patients with airway symptoms and/or emesis referred for evaluation. All underwent polysomnography and single-channel pH probe.	Apnea	32-57	<ul style="list-style-type: none"> <li>Nonstandard definition of reflux: sudden fall in pH with the end of an episode defined as a rise in pH above 4.</li> </ul>
Phipps et al, <sup>24</sup> 2000	30 Consecutive patients aged 2-18 y, in whom treatment for CT-confirmed sinusitis had failed. All underwent dual-channel pH probe testing.	Chronic sinusitis	63 With GER, 20 with nasopharyngeal reflux	<ul style="list-style-type: none"> <li>Reflux was defined as pH &lt;4 for 4.19% of monitored time.</li> <li>Included patients with known reflux.</li> </ul>
Stroh et al, <sup>64</sup> 1998	24 Patients referred for airway evaluation and rigid esophagoscopy with biopsy.	Stridor, apnea, chronic cough	54	<ul style="list-style-type: none"> <li>Reflux was defined by pathologic findings on biopsy.</li> <li>No comments were made on costs or safety of procedure for diagnosis vs pH probe.</li> </ul>
Veereman et al, <sup>65</sup> 1991	49 Of 130 patients underwent 24-h single-channel pH probe and sleep study.	ALTE immediately after eating	69	<ul style="list-style-type: none"> <li>Authors used their own reflux definition scoring system and did not explain rationale.</li> </ul>
Vijayarajnam et al, <sup>66</sup> 1999	116 Patients with history of vomiting (n = 54), apnea, ALTE, or choking (n = 62). All underwent dual-channel 24-h pH probe testing.	Apnea, choking, ALTE, stridor	100 Proximal, 75 distal reflux	<ul style="list-style-type: none"> <li>Reflux was defined as pH &lt;4 for more than 5% of study time.</li> </ul>
Walner et al, <sup>67</sup> 1998	74 Patients who underwent pH probe testing (74 single channel, 55 dual channel).	Subglottic stenosis	50 (By distal probe), 88 (by proximal probe)	<ul style="list-style-type: none"> <li>Reflux criteria for the upper and lower probe included percentage of time with pH &lt;4.0; however, no specific cutoff was used for positivity.</li> </ul>
Yellon et al, <sup>68</sup> 2000	101 Patients undergoing esophageal biopsy; all had undergone previous reflux testing.	Cough, apnea, sinusitis, stridor	63-100	<ul style="list-style-type: none"> <li>Reflux was diagnosed by esophageal biopsy.</li> <li>Statistically significant excess of reflux by biopsy (all <math>P &lt; .04</math>) 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).</li> <li>No correlation between histologic findings and degree of reflux diagnosed via standard methods.</li> </ul>
Zallesska-Krecicka et al, <sup>69</sup> 2002	100 Patients with gastrointestinal symptoms and at least 1 other respiratory symptom; all underwent dual-channel pH probe.	Recurring hoarseness, chronic cough, throat clearing, recurrent sore throat	90	<ul style="list-style-type: none"> <li>Reflux was defined as mild, moderate, severe based on number of reflux episodes, percentage of time with a pH &lt;4, and DeMeester score. No clear cutoff for "normal."</li> </ul>

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).

ods 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<sup>78</sup> and Newman et al,<sup>74</sup> 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.

## COMMENT

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

Source	Study Description	Symptoms	Findings (Control vs Symptomatic)	Reflux Definition/Study Comments
de Ajuriaguerra et al, <sup>70</sup> 1991	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.	Apnea	33% vs 71%; <i>P</i> value not provided.	<ul style="list-style-type: none"> <li>Pathologic reflux was defined as pH &lt;4 for 10.4% of recording time.</li> <li>Mean duration of reflux in both groups appeared similar.</li> </ul>
Bibi et al, <sup>71</sup> 2001	116 Patients undergoing bronchoscopy. Controls ( <i>n</i> = 62) had chronic respiratory symptoms refractory to medical therapy, persistent infiltrates, or suspected foreign body. Symptomatic patients ( <i>n</i> = 54) had a history of vomiting, feeding related cough, or cough not responding to treatment. All underwent reflux testing via combination of modalities.	Laryngomalacia, tracheomalacia	37% vs 75% by pH results only; <i>P</i> value was not significant. 39% vs 90% when reflux tests combined; <i>P</i> < .05.	<ul style="list-style-type: none"> <li>Reflux was defined as pH &lt;4.0 for &gt;8% of study duration, or reflux to upper esophagus was seen on barium swallow.</li> <li>Reflux and laryngotracheomalacia were statistically associated (<i>P</i> &lt; .05) only when results of reflux tests (barium swallow or pH probe) were combined.</li> <li>Single probe pH testing may have reduced sensitivity of their findings.</li> </ul>
Carr et al, <sup>72</sup> 2001	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.	Adenoid hypertrophy	7% vs 42%; <i>P</i> < .01.	<ul style="list-style-type: none"> <li>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.</li> </ul>
Contencin and Narcy, <sup>23</sup> 1991	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.	Rhinopharyngitis, otitis media	Pharyngeal reflux episodes with pH <6, 2.3 vs 9.2; <i>P</i> < .05. Time with pH <6, 1.1% vs 18.7%; <i>P</i> < .05.	<ul style="list-style-type: none"> <li>Authors chose nasopharyngeal pH &lt;6 as definition of reflux.</li> <li>Results are not reported using a positivity cutoff.</li> <li>"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.</li> </ul>
Contencin and Narcy, <sup>73</sup> 1992	8 Of 14 consecutive patients referred for recurrent croup compared with 6 patients with neck infections. All underwent dual-channel 24-h pH probe.	Croup	20% vs 62% esophageal reflux; <i>P</i> < .05. 20% vs 100% nasopharyngeal pH monitoring; <i>P</i> < .05.	<ul style="list-style-type: none"> <li>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.</li> </ul>
Little et al, <sup>17</sup> 1997	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.	Hoarseness, stridor, apnea	Mean acid exposure 5.1% vs 7.3% ( <i>P</i> = .001).	<ul style="list-style-type: none"> <li>Reflux severity was reported as differences in mean acid exposure time.</li> <li>No comparisons with nonrespiratory group were provided, though differences are likely to exist.</li> </ul>

(continued)

logic flaws related to inconsistent methods used for diagnosing reflux, biased patient populations, and limited statistical methods.

### THE DIAGNOSIS OF REFLUX

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.<sup>18,79,80</sup> Although reproducibility of pediatric 24-hour dual-channel pH probe results has been questioned<sup>81</sup> 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,<sup>82,83</sup> but they demonstrate sensitivities and specificities lower than dual-channel pH probe.<sup>84,85</sup>

Investigators have tried alternate diagnostic testing to aid diagnosis of reflux. Laryngoscopy and bronchos-

copy findings—especially arytenoid edema, postglottic edema, and lingual tonsillar hypertrophy—have been demonstrated to correlate with acid exposure.<sup>45,54</sup> 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.<sup>64,68</sup> 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 (cont)**

Source	Study Description	Symptoms	Findings (Control vs Symptomatic)	Reflux Definition/Study Comments
Newman et al, <sup>74</sup> 1989	97 Consecutive patients with ALTE referred for evaluation compared with 22 coconsecutively evaluated patients with recurrent emesis, regurgitation, or poor weight gain but no pulmonary symptoms. All underwent single-channel 24-h pH probe testing.	ALTE	Reflux, 86% vs 77%; <i>P</i> value was not significant. Postprandial reflux, 10% vs 52%; <i>P</i> < .001. Sleep reflux, 0% vs 27%; <i>P</i> < .001.	<ul style="list-style-type: none"><li>• Positive reflux test results were defined using criteria of Sondheimer<sup>75</sup> and Spitzer et al.<sup>76</sup></li><li>• Authors do not present results comparing ALTE patients with classic GER patients.</li><li>• Patients with ALTE are older (2.8 vs 0.9 mo) and appear to have a similar sex mix. No other characteristics or <i>P</i> values are given, but the authors report that these numbers are not different.</li></ul>
Sacre and Vandenplas, <sup>77</sup> 1989	4 Groups of patients prospectively evaluated: 62 with ALTE; 387 control patients referred for SIDS screening, 60 of whom had reflux symptoms and 76 of whom had respiratory dysfunction during sleep. All patients underwent 24-h single-channel pH probe.	ALTE	Patients with SIDS, 8.5%. Patients with ALTE, 42%. Patients with reflux symptoms (100%). Patients with sleep dysfunction (43%).	<ul style="list-style-type: none"><li>• Reflux defined using a reflux index, a measure based on the percentage of time with a pH &lt; 4, combined with normative data (number of reflux episodes exceeding the mean ± 3 SD of age-matched data).</li><li>• No <i>P</i> values were provided for intergroup comparisons.</li></ul>
See et al, <sup>78</sup> 1989	16 Patients referred after ALTE compared with 6 age-matched controls with vomiting resulting in poor weight gain. All underwent 16-20-h single-channel pH probe testing, pulse oximetry, and transthoracic impedance pneumocardiography.	ALTE	Number of esophageal reflux episodes, 26.5 vs 28.8; <i>P</i> value was not significant. Nocturnal reflux, 40% vs 70%; <i>P</i> < .001. Oxygen desaturation during feeding, 0% vs 50%; <i>P</i> < .001.	<ul style="list-style-type: none"><li>• Reflux was defined as pH &lt; 4 for &gt; 12 minutes in 2 hours after feeding, pH &lt; 4 for ≥ 30 s for ≥ 2 episodes in third postprandial hour, esophageal pH &lt; 4 for ≥ 4 min while sleeping.</li><li>• Groups were age matching by <math>\chi^2</math> test. Patients with ALTE had less vomiting, more apnea and muscle tone problems, choking symptoms.</li></ul>
Spitzer et al, <sup>76</sup> 1984	15 Patients with awake apnea compared with 9 controls (3 siblings of patients with SIDS, 3 with a history suggestive of reflux). All underwent 24-h single-channel pH probe.	Apnea	11% vs 100%; <i>P</i> value was not provided.	<ul style="list-style-type: none"><li>• Reflux positivity was defined as pH &lt; 4 for ≥ 10% of the first 2 postprandial hours, pH &lt; 4 for 15 s in ≥ 2 episodes in the third hour, reflux during sleep, reflux with airway obstruction.</li><li>• Patients were generally similar in age, birth weight, and sex, but no statistical tests were used.</li></ul>

Abbreviations: ALTE, acute life-threatening event; GER, gastroesophageal reflux; SIDS, sudden infant death syndrome.

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.<sup>3</sup> 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.<sup>9</sup> However, other studies showing no impact of reflux treatment on airway surgery for subglottic stenosis have refuted this finding.<sup>86</sup>

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

development rather than site of care (ie, pediatric intensive care unit or referral for reflux tests on the basis of an alternate diagnosis). Admittedly, the identification and selection of controls may be difficult, but in the absence of an ideal group, adherence to standards of reporting that clinicians can use to make decisions about treatment should be the minimal standard. For example, many of the studies in our review were based at tertiary care centers and were likely subject to substantial referral bias. Few studies provided any patient information other than age or sex, making it nearly impossible to discern whether results from these studies could be used by non-tertiary care-based clinicians.<sup>87-89</sup> In addition to being potentially helpful in multivariable models by producing adjusted results, detailed information about patients' comorbidities would be useful for clinicians simply seeking to apply evidence to their practices.

## 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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