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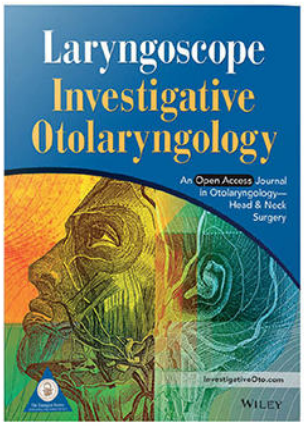

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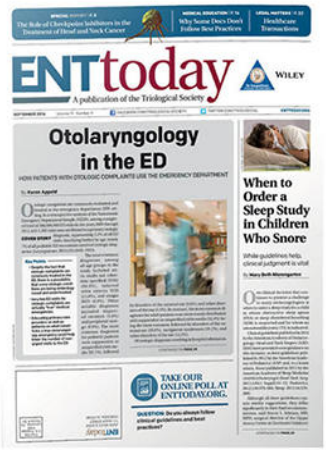

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The Relationship between Croup and Gastroesophageal Reflux: A Systematic Review and Meta-Analysis

Alanna Coughran, MD; Karthik Balakrishnan, MD, MPH; Yifei Ma, MA, MS; Reza Vaezeafshar, MD; Nicole Capdarest-Arest, MA(LIS); Osama Hamdi, BS; Douglas R. Sidell, MD

Objective: The mechanism by which recurrent croup occurs is unknown. Gastroesophageal reflux is commonly implicated, although this relationship is only loosely documented. We conducted a systematic review with a meta-analysis component to evaluate the relationship between recurrent croup and gastroesophageal reflux disease (GERD), and to assess for evidence of improvement in croup symptoms when treated.

Style Design: Systematic Review and Meta Analysis.

Methods: We searched five separate databases. Studies were included if they discussed the relationship between croup and GERD in children, >5 subjects, and available in English. Literature retrieved was assessed according to pre-specified criteria. Retrieved articles were reviewed by two independent authors and decisions mediated by a third author. If there was a difference of opinion after first review, a second review was performed to obtain consensus. Heterogeneity was calculated and summarized in forest plots.

Results: Of 346 initial records, 15 met inclusion criteria. These were two retrospective cohort and 13 cross-sectional studies. Thirteen of 15 articles support an association between recurrent croup and GERD. Although heterogeneity is high among studies that reported prevalence of GERD, there is less uncertainty in results for improvement to recurrent croup after GERD treatment. Most studies lacked a control group and all carry a moderate-to-high risk of bias.

Conclusion: There is limited evidence linking GERD to recurrent croup; Further research is needed to assess for causality as most studies are retrospective, lack a control group, and have a study design exposing them to bias. Patients treated with reflux medication appear to demonstrate a reduced incidence of croup symptoms.

Key Words: Pediatric airway, reflux, croup.

Level of Evidence: 1

***Laryngoscope*, 00:1–9, 2020**

INTRODUCTION

Laryngotracheobronchitis, or croup, is thought to have a lifetime prevalence of 15%[1] and to account for 41,000 hospital admissions annually in the United States.[2] The term "recurrent croup" has carried many definitions but is typically used to describe patients who have greater than two or three episodes of croup,[3,4] and it has a lifetime prevalence of 5%.[1] The causal factors of recurrent croup have not been firmly established, and many different mechanisms for recurrent croup have been proposed. These include esophageal reflux, undiagnosed subglottic narrowing, esophageal disorders such as eosinophilic esophagitis and other inflammatory disorders, and airway hyperreactivity.[5] Reflux is of particular interest given its high prevalence. Additionally, there is a plausible potential biologic mechanism linking esophageal reflux to recurrent croup; tracheal aspiration of refluxed material may damage the mucosal barrier of the trachea, increasing susceptibility to infection.[6]

Although reflux has been implicated in the pathogenesis of recurrent croup in several studies, a methodical investigation critically appraising and synthesizing these studies has not yet been performed. In this study, we examine whether there is an association between a diagnosis of gastroesophageal reflux disease and a diagnosis of recurrent croup. Our secondary question is, are anti-reflux medications associated with improvement to recurrent croup in pediatric patients, compared to patients with recurrent croup not treated for gastroesophageal reflux?

METHODS

The PRISMA strategy was used for this study.[7]

Data Sources and Search Strategies

A systematic review protocol was developed based on predetermined aims and objectives. The PICO question that guided the search strategy was, in pediatric patients, is there an association between a diagnosis of gastroesophageal reflux disease and a diagnosis of recurrent croup? For the same population, we also

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investigated a secondary outcome of interest to understand if anti-reflux medications are associated with improvement to recurrent croup in pediatric patients, compared to patients with recurrent croup not treated for gastroesophageal reflux.

We conducted a systematic review of the literature by searching MEDLINE (via PubMed and Ovid), Scopus, PsycINFO, CINAHL, and Web of Science databases. To identify relevant articles, two authors (DRS and RV) independently reviewed the query strategy, which was developed by a professional librarian (NCA). MEDLINE was searched using MeSH terms and keywords via the following strategy: ("Croup"[Mesh] OR croup[tiab] OR laryngotracheitis[tiab] OR "atypical croup"[tiab] OR (croup[tiab] AND (spasmodic[tiab] OR nocturnal[tiab] OR "spasmodic nocturnal"[tiab])]) AND ("Gastroesophageal Reflux"[Mesh] OR "gastroesophageal reflux"[tiab] OR "gastro-oesophageal reflux"[tiab] OR "gastro-esophageal reflux"[tiab] OR esophagitis[tiab] OR oesophagitis[tiab] OR "Esophagitis"[Mesh] OR "Eosinophilic Esophagitis"[Mesh] OR "Esophagitis, Peptic"[Mesh] OR "Laryngopharyngeal Reflux"[Mesh] OR "Laryngopharyngeal Reflux"[tiab] OR "Laryngismus"[Mesh] OR laryngospasm[tiab]). Other database searches were constructed with similar search terms. These searches identified 346 records for possible inclusion. Literature review and analysis was completed through May, 2019.

Study Selection

After deduplication, 212 records remained for title/abstract screening. Independent examination by DRS and RV of the titles and abstracts of these records identified 27 articles for potential inclusion and for which we obtained the full texts for more in-depth evaluation. To make selections at this level, we first identified all articles mentioning both croup and GERD and their interrelationship, regardless of publication date. Articles that did not mention both croup and GERD and their interrelationship were excluded. Next, we used predetermined criteria to evaluate the 27 full-text articles, excluding all case reports and studies with fewer than five subjects, studies without pediatric patients, articles not available in English, and those without human subjects. Articles retrieved were reviewed by two independent authors (DRS and RV) and decisions mediated and collected by NCA. If there was a difference of opinion after first review, consensus was obtained through a second review.

Data Extraction

Data was extracted into a spreadsheet independently and in duplicate by two authors (RV and AC). Variables that were included in this extraction process were participants, interventions, comparisons, outcomes, and study design including presence of a control group. Principal summary measures were the prevalence of GERD or prevalence of recurrent croup and percent of patients reporting a change in respiratory symptoms after anti-reflux treatment, as well as odds ratios associating reflux with history of recurrent croup.

Statistical Analysis

Higgins' heterogeneity index (I^2) was manually calculated for those studies that reported prevalence of GERD and for those studies that reported improvement in recurrent croup symptoms

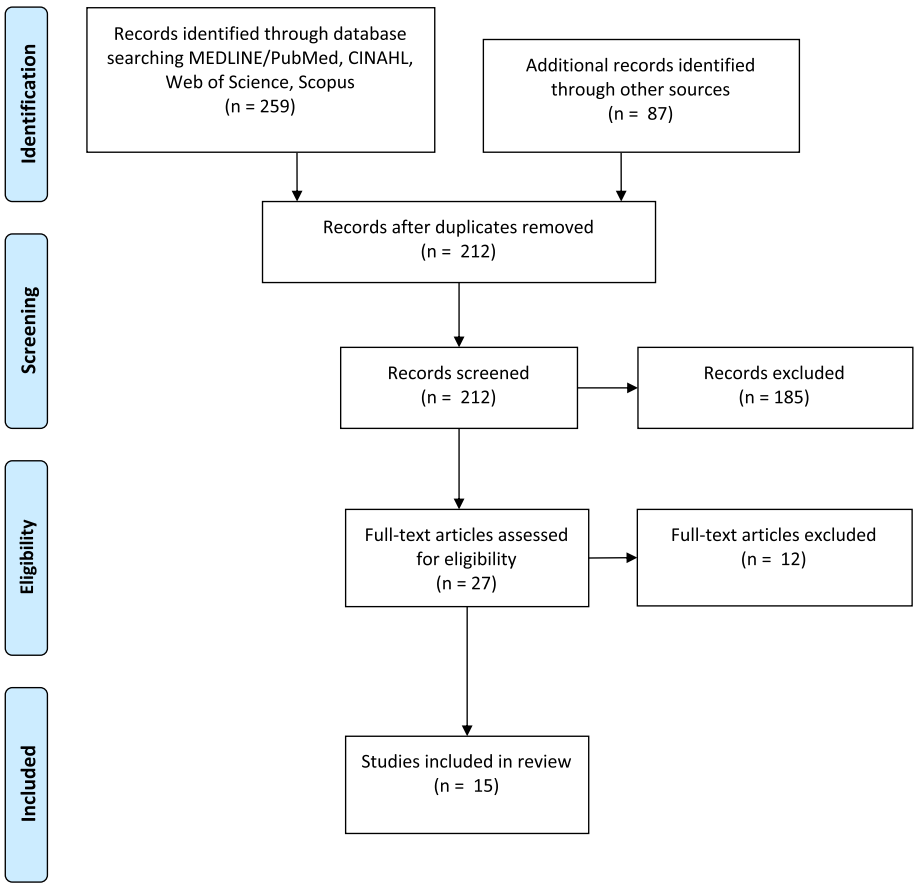

Fig. 1. Flow diagram. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE I.
Studies Investigating the Prevalence of GERD in Patients with Recurrent Croup.

Author and year	Type of study	No. of patients	Mean age (yr)	Definition of recurrent croup	Definition of GERD	Control group	No. in control group	Outcome measure	Findings
Arslan 2009	Retrospective cohort	32	4.4	≥3 episodes	Symptoms of gastroesophageal reflux disease	First episode of croup	25	Difference in % with GERD symptoms	62.5% of children with RC had GERD symptoms vs. 16% in control group
Contencin 1992	Retrospective cohort	8	3.6	≥3 episodes	Esophageal and pharyngeal pH monitoring	Patients hospitalized for neck surgery or infection	6	Difference in % with GERD diagnosis	62.5% of patients with RC had a pathologic fraction of time with esophageal and pharyngeal pH < 4, compared to 16.7% of controls
Cooper 2012	Cross-sectional	80	4.8	Numerous recurrent episodes or outside typical age group	Prior diagnosis, prior response to PPI, pH probe study results, or esophagoscopy biopsy results	-	-	% with GERD	38.8% of patients with RC had signs of GERD
Delany 2015	Cross-sectional	103	3.4	≥2 episodes	Prior diagnosis of GERD by an otolaryngologist or other provider	-	-	% with GERD	60.2% of patients with RC had history of GERD
Duval 2015	Cross-sectional	235	4.1	≥2 episodes in 1 year or ≥ 3 lifetime episodes	Bronchoscopy suggestive of GERD	-	-	% with GERD	47.2% of patients with RC had signs of GERD
Farmer 2001	Cross-sectional	53	2 (median)	Recurrent intermittent airway obstruction	Upper aerodigestive tract endoscopy consistent with GERD	-	-	% with GERD	18.9% of patients with RC had signs of GERD
Hoa 2008	Cross-sectional	47	1.7	≥2 episodes	Direct laryngoscopy and bronchoscopy suggestive of GERD	-	-	% with GERD	87.2% of patients with RC had GER-related changes, 21.3% had prior diagnosis of GER
Jabbour 2011	Cross-sectional	81	3.4	Not given	Direct laryngoscopy and bronchoscopy suggestive of GERD	-	-	% with LPR	4.9% of patients with RC had LPR
Kwong 2007	Cross-sectional	17	3.9	≥2 episodes	Direct laryngoscopy and bronchoscopy suggestive of GERD	-	-	% with GERD	82.3% of patients with RC had endoscopic evidence of GER, 35% had prior diagnosis of GERD
Rankin 2013	Cross-sectional	90	4.5	≥2 episodes	Direct laryngoscopy and bronchoscopy consistent with GERD, esophageal pH studies, barium studies	-	-	% with GERD	27.8% of patients with RC had endoscopic findings, pH, or barium suggestive of reflux
Waki 1995	Cross-sectional	32	Not Given	≥2 hospitalizations for croup	Gastroesophageal reflux scintiscan, direct laryngoscopy and bronchoscopy consistent with GERD	-	-	% with GERD	47% of patients with RC had signs of GERD
Yellon 2000	Cross-sectional	16	1.8	Not given	Esophageal biopsy consistent with esophagitis	-	-	% with GERD	75% of patients with RC had GERD per biopsy
Hodnett 2015	Cross-sectional	197	4.4	Not given	Esophageal biopsy consistent with reflux esophagitis	-	-	% with GERD	8.8% of patients with RC had signs of GERD

(Continues)

TABLE I.
Continued

Author and year	Type of study	No. of patients	Mean age (yr)	Definition of recurrent croup	Definition of GERD	Control group	No. in control group	Outcome measure	Findings
Duval 2016	Cross-sectional	117	Not Given	≥2 episodes in lifetime	24-h pH probe, esophageal biopsy and/or upper gastrointestinal radiographic study	-	-	% with GERD	59% of patients with RC had signs of GERD
Munson 2016	Cross-sectional	6	1	≥2 episodes in lifetime	Not stated	-	-	-	100% (All patients reported had GERD and croup)

GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; RC = recurrent croup.

for patients treated with anti-reflux medications. SAS 9.4 Modeling software (SAS Institute, Cary, NC) was used to calculate the odds ratio of having GERD in two retrospective cohort studies. Forest plots were generated to summarize these heterogeneity results.

Assessing Risk of Bias

Risk of bias was assessed at the study level using the Newcastle-Ottawa scale.[8] Risk of bias for retrospective cohort studies was based on consideration of differential loss to follow-up, minimization of potential confounders, and matching of subjects in the exposed cohort and comparison group. Case matching was assessed by comparing demographic factors and medical history for cases and control groups, including factors reported by study authors such as age, gender, duration of symptoms, and number of hospitalizations. For cross-sectional studies, we evaluated each study for consideration of loss to follow-up rate and attempts made to reduce recall bias and misclassification bias. We also evaluated each study for generalizability and considered publication bias as a factor potentially affecting the cumulative evidence. A flow diagram outlining the study selection is shown in Figure 1.

Reflux Therapy and Incidence of Croup. All studies demonstrating a relationship between the incidence of croup and reflux were further assessed to determine if the management of GERD symptoms with anti-reflux therapy had an effect on croup symptoms.

RESULTS

From the 27 articles identified through title and abstract review, 12 were excluded according to our preset criteria (Fig. 1). The remaining 15 studies were included for full-text review with a total of 1435 participants. The collected studies defined recurrent croup in variable ways. The most common definition was greater than or equal to two or three episodes of croup in a lifetime. There was also wide variation in the definition of gastroesophageal reflux disease (Table I).

Of the 15 articles included in this review, 12 are cross-sectional studies that describe the prevalence of reflux in patients with recurrent croup.[3,4,6,9–19] These are summarized in Table I. The reported prevalence of GERD in these studies ranges from 5% (Jabbour et al.) to 87% (Hoa et al.), and studies that used direct laryngobronchoscopy findings to define GERD tended to report higher prevalence than those that relied on clinical presentation and history.[10] Notably, 10 out of 12 of these publications do not include a control group, and they are further limited by the fact that 6 of the 12 do not have clear inclusion and exclusion criteria making it difficult to evaluate generalizability. Risk of bias is shown in Table II and is moderate to high across all studies, with a most frequently reported NOS score of 3 out of a maximum of 7. No study was scored above 5. Analysis of heterogeneity (I^2) of these studies resulted in I^2 of 97% and is presented in Figure 2.

Two of the 12 retrospective studies examining the prevalence of GERD in patients with recurrent croup do include a control group and present a statistically robust analysis (Table I). Arslan et al. compared patients with a history of at least three episodes of croup to patients with

TABLE II.
Quality Assessment of Studies using a Newcastle-Ottawa Scale for Assessing Studies in the Systematic Review of GERD and Recurrent Croup.

Newcastle-Ottawa for cross sectional studies

	Selection				Comparability	Outcome		
Study ID	Representativeness of sample	Sample size	Ascertainment of exposure to acid reflux	Non-respondents	The subjects in different outcome groups are comparable, confounders are controlled	Assessment of outcome, diagnosis of croup	Adequacy of statistical analysis	Total
Carr 2000	1	0	1	0	0	0	1	**3**
Cooper 2012	1	1	0	1	0	1	1	**5**
Delany 2015	0	1	0	0	0	1	1	**3**
Duval 2015	0	1	1	1	0	0	1	**4**
Farmer 2001	0	1	1	0	0	0	0	**2**
Kwong 2007	0	0	1	0	0	0	0	**1**
Hoa 2008	0	0	1	1	0	1	0	**3**
Jabbour 2011	0	1	0	0	0	1	1	**3**
Krishnan 2015	1	1	1	1	0	0	1	**5**
Rankin 2013	1	0	1	1	0	0	1	**4**
Suskind 2001	0	1	1	1	0	0	0	**3**
Yellon 2000	0	0	1	0	0	0	1	**2**
Waki 1995	0	0	1	0	0	0	0	**1**

Newcastle-Ottawa for cohort studies

	Selection					Outcome		
Study ID	Representativeness of exposed cohort	Selection of non exposed cohort	Ascertainment of exposure to acid reflux	Diagnosis of croup not present at start of study	Comparability Study controls for confounders	Assessment of outcome, diagnosis of croup	Adequacy of follow up and accounting for loss to follow up	Total
Arslan 2009	1	1	1	1	0	1	0	**5**
Contencin 1992	0	0	1	0	0	0	0	**1**

GERD = gastroesophageal reflux disease.

a history of one episode and found that patients with recurrent croup were significantly more likely to have symptoms of GER including vomiting ($P = .02$) and regurgitation ($P = .007$).[11] However, the control group in this study may have inadvertently included participants that will go on to develop recurrent croup; this potential misclassification bias would result in an underestimation of the association of GERD symptoms with history of recurrent croup. The second study to include a control group, by Contencin and Narcy, used esophageal and pharyngeal pH monitoring to establish that patients with recurrent croup are more likely to have pharyngeal and esophageal reflux compared to patients without recurrent croup, with the average lowest pharyngeal pH 4.43 in cases and 5.5 in controls ($P = .005$).[4] However, an important limitation of this study is the small sample size of eight patients and six controls. Meta-analysis of these two studies as shown in Figure 3 showed that the combined odds ratio of having GERD for patients with recurrent croup is 8.6.

Of the 12 studies specifically investigating prevalence of reflux in patients with recurrent croup, three additionally report improvement of respiratory symptoms in patients with recurrent croup after treatment with anti-reflux medications.[3,10,12] This is shown in Table III. The proportion of responding patients ranged from 77% (Kwong et al.) to 91% (Rankin et al.). Specifically, one study found that 87.5% of patients reported improvement to croup symptoms after treatment with

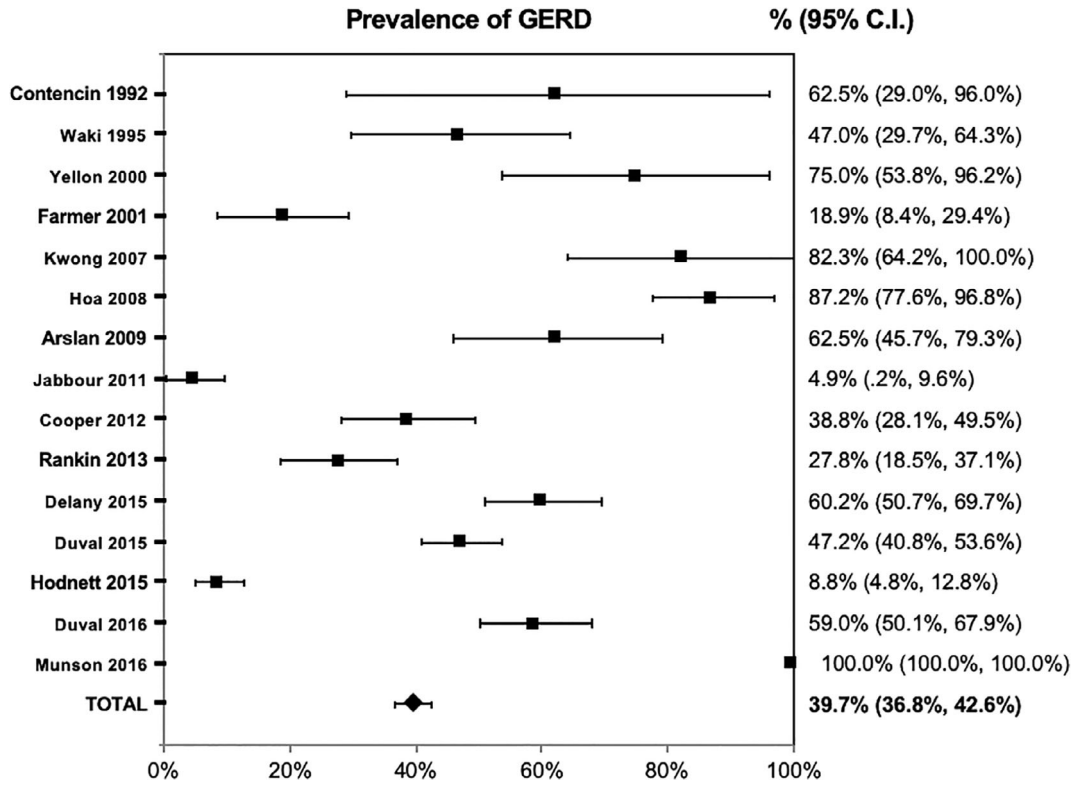

Fig. 2. Prevalence of GERD. The prevalence of GERD in patients with recurrent croup has a range of 5% to 87%. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.[20,21] GERD = gastroesophageal reflux disease.

ranitidine and metoclopramide for a 6–9-month course.[10] Another study found that 90.9% reported improvement after treatment with ranitidine or omeprazole for an unknown duration,[3] and two studies reported improvement after an anti-reflux treatment regimen that was not described.[12,22] Additionally, one study showed improvement to upper airway symptoms after anti-reflux surgery.[22] As shown in Figure 4, meta-analysis of these results shows that 83.8% of patients treated for GERD showed improvement to recurrent croup symptoms, with $I^2 = 0$.

Further analysis of combined data demonstrates that of the 154 patients with croup, 78 (49.4%) have laryngeal findings consistent with GERD. Sixty-eight of these patients were treated with anti-reflux medication and improvement of croup was observed in 58 (85.3%).

An additional study investigating six patients with recurrent croup and reflux reported an improvement in

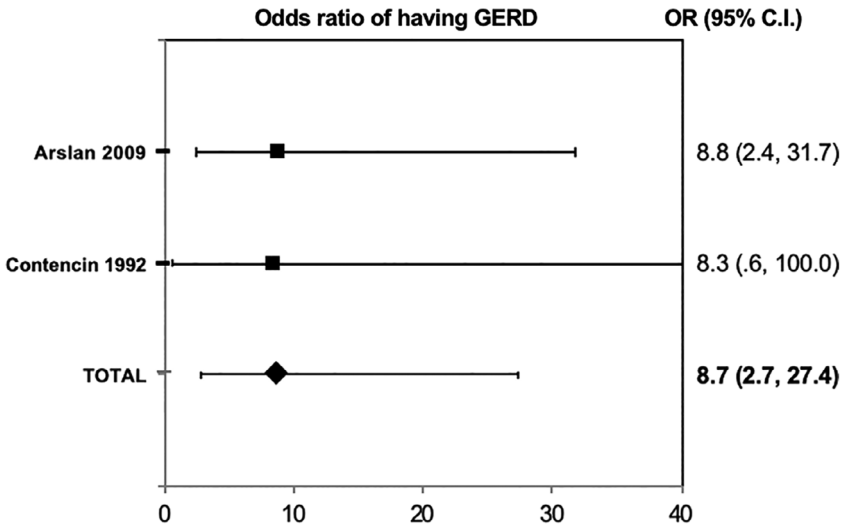

Fig. 3. Odds ratio of having GERD. GERD = gastroesophageal reflux disease.

TABLE III.
Studies Investigating the Changes to Symptoms of Recurrent Croup Following Treatment with Anti-reflux Medications.

Author and year	Hoa 2008	Kwong 2007	Rankin 2013	Munson 2016
No. of patients total	47	17	90	6
No. of patients treated	40	17	11	6
Medication	Ranitidine + metoclopramide x6–9 months	Not stated	Ranitidine or omeprazole, duration not stated	Not stated
Definition of improvement to recurrent croup	Patient-reported severity and frequency of symptoms	Patient-reported shortened duration of croup-like episodes, decreased symptom severity, or becoming asymptomatic	Patient-reported decreased symptom severity, decreased frequency of episodes, or resolution of symptoms	Not stated
% with improvement to recurrent croup	87.5%	76.5%	90.9%	67%

recurrent croup symptoms of four of the six patients. Because GERD was not defined and an objective measure of improvement following anti-reflux treatment was not identified, this study was not included in this analysis.[22] One limitation of these studies is that only one, Hoa et al., clearly states the anti-reflux medication regimen (ranitidine + metoclopramide for 6–9 months) that led to improvement.[12] Another limitation is that these three studies do not mention recording adverse events related to anti-reflux medications and do not include a control group.

One study in the group of retrospective case series calculating prevalence of GERD in patients with recurrent croup, Waki et al., includes an analysis of the severity of recurrent croup and states that as the number of hospitalizations increases to three or more, the prevalence of GERD increases from 47% to 63%.[6] This suggests a link between the two illnesses but does not establish causality.

Jabbour et al., another retrospective case series of similar design, had different results, reporting that the prevalence of laryngopharyngeal reflux in patients with recurrent croup was as low as 4.9%.[16] It is one of two studies included in our review that does not support a link between reflux and recurrent croup, although recurrent croup as well as inclusion and exclusion criteria were not clearly defined, producing susceptibility to selection bias.

The remaining three papers sought to establish a causal link between recurrent croup and GERD. Suskind et al. did a retrospective case review of 14 patients with upper airway abnormalities (subglottic stenosis, subglottic edema, reflux apnea, and recurrent croup) and found that all 14 experienced resolution of their upper airway symptoms after anti-reflux surgery. However, they did not specify how many of those patients had recurrent croup in particular, and they are susceptible to selection bias as patients were excluded if their otolaryngologic symptoms were thought to be unrelated to reflux.[23] Krishnan et al. found a statistically significant positive association (P = .0385) between a marker of extra-esophageal reflux disease (positive pepsin assay on tracheal aspirates) and history of recurrent croup in a cross-sectional study with clearly described study design.[24] The final study included in our review, Carr et al., compared prevalence of recurrent croup in patients with GERD compared to patients without GERD and found no difference between the two groups, in a study

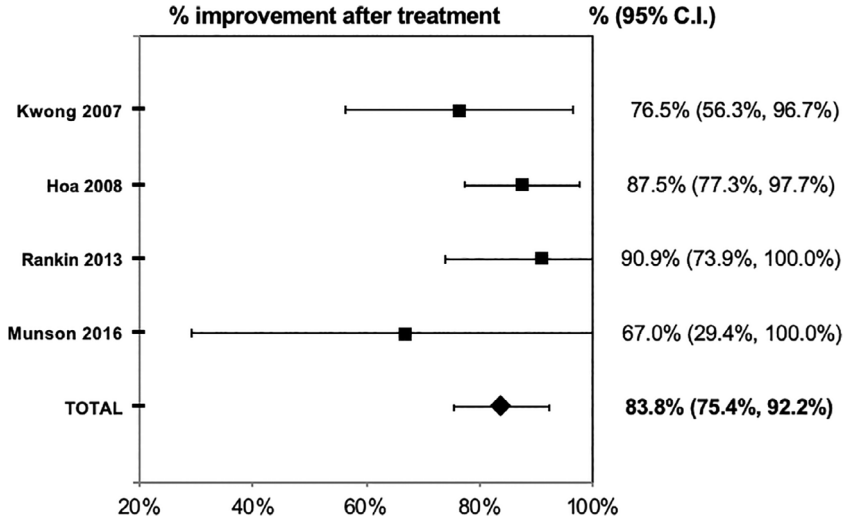

Fig. 4. Percent improvement after treatment.

with clearly defined inclusion and exclusion criteria.[25] Like all cross-sectional studies, Carr et al. is susceptible to attrition and recall bias, and the authors do not address if any participants were lost to follow-up.

Overall the studies were found to be generalizable only to a specific group of patients referred for recurrent croup who had already undergone endoscopy as part of their work up, and not generalizable to patients without a diagnosis of recurrent croup or whose other symptoms collectively did not warrant laryngobronchoscopy or esophagoscopy.

DISCUSSION

There is limited evidence that, for pediatric patients, there is an association between a diagnosis of GERD and a diagnosis of recurrent croup. The majority of publications (12 out of 15) are retrospective case series or cohort studies that do not include a control group and use simple descriptive statistics to report their findings. All but one of these retrospective studies reports a high prevalence of reflux disease in patients with recurrent croup; however, high heterogeneity on meta-analysis limits our ability to draw conclusions from these studies. Two case–control studies, Arslan et al. and Contencin and Nancy, found a statistically significant increase in reflux in patients with recurrent croup, from a symptomatic standpoint and with esophageal and pharyngeal pH data.[4,11] However, regardless of study design, this association does not establish causality. Patients treated with reflux medications appear to demonstrate a reduced incidence of croup or croup symptoms, and these studies are less heterogeneous, meaning that the combined results are more conclusive.

The studies that provide the strongest evidence in support of a causal link between reflux disease and recurrent croup are those that show an improvement to recurrent croup after treatment with antireflux medications,[3,10,12] and a study that showed improvement to upper airway symptoms after antireflux surgery.[23] Although only one of these studies describes the exact antireflux medication regimen that was used, the external validity of these studies is strengthened by the proposed mechanism that aspiration of refluxed material may damage the mucosal barrier of the trachea. Furthermore, meta-analysis of these results also shows improvement after treatment, with heterogeneity of these studies was equivalent to 0, making the combined analysis of the results more meaningful.

This systematic review has focused on the association between GERD and recurrent croup; additionally, some studies included in this review investigated additional potential causes of recurrent croup. Both Kwong et al. and Cooper et al. investigated large airway lesions in addition to reflux as potential etiologies of recurrent croup. Kwong et al. noted that all 14 patients in their study who had signs of gastroesophageal reflux also had subglottic stenosis, and Cooper et al. found that 31 out of 80 patients with recurrent croup had a large airway lesion diagnosed on endoscopy, including subglottic stenosis, subglottic hemangiomas, tracheomalacia, laryngomalacia, and other abnormalities.[12,13] Both Arslan et al. and Cooper et al. investigated the prevalence of atopy in patients with recurrent croup, respectively finding that 5 out of 32 patients had skin test positivity, and 35 out of 80 had self-reported atopic conditions.[11,13] These findings are subject to the same biases discussed above, but it is important to note these findings which support a multifactorial etiology of recurrent croup.

As a systematic review, this analysis does not overcome limitations in the design and implementation of the included studies. Importantly, there is variability in criteria used to categorize patients as having recurrent croup in the papers included in this systematic review, making it difficult to generalize results. The most widely cited definition of recurrent croup is two or more lifetime episodes of acute-onset stridor, barking cough, and hoarseness[3,10,12,14,15] requiring hospitalization.[6] However, neither Jabbour et al. nor Yellon et al. provided a definition for recurrent croup in their study.[16,17] Others required a cutoff of three or more episodes.[4,11] This inconsistent definition may lead to patients misclassified as having recurrent croup, which would underestimate the link between reflux and recurrent croup, or vice versa if they are misclassified as controls. Furthermore, the included studies range widely in their definition of GERD, further limiting attempts to generalize results. Most studies did not use esophagoscopy with biopsy or pH monitoring, the gold standard, to establish a diagnosis of GERD. The most commonly used criteria was direct laryngoscopy with findings consistent with GERD, such as erythema and edema of the arytenoids and posterior glottis, visualized active reflux, or esophageal strictures.[3,6,10,15,16] Other studies defined GERD as a history of reported symptoms of reflux disease.[11,14] Additionally, two of four papers (Kwong et al. and Munson et al.) that reached the conclusion that GERD treatment improves croup symptom did not state what treatment was used in their study. Although it would be clinically relevant to know the exact GERD treatment used in these studies, we included these studies because they are relevant to systematically reviewing the known literature on this topic.

Finally, in our database search we retrieved published literature and therefore cannot correct biases that occur in the publication process, including a bias towards the publication of positive results showing a link between reflux and recurrent croup.

CONCLUSION

Overall, the majority of studies included in this review were heterogeneous in design, definitions, and outcomes, and were lacking a control group. Although meta-analysis of reports included herein demonstrate that the prevalence of GERD is about 40% among patients with recurrent croup, these results are difficult to interpret because of the high heterogeneity of the included reports, and without knowledge of the prevalence of GERD in healthy controls. There are also promising findings in a subset of manuscripts in this review which demonstrate that patients with recurrent croup will have improvement

in symptoms following treatment with anti-reflux medications or surgery, and this is supported by a meta-analysis showing improvement and low heterogeneity across studies. Unfortunately, small sample sizes in these studies limit the strength of this association.

Ultimately, well-designed prospective trials of anti-reflux medications or surgery in patients with recurrent croup are necessary to elucidate the presence or absence of a causal link between GERD and recurrent croup, and whether the benefits of such interventions outweigh any inherent treatment risks.

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