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# A systematic review of the evidence on spontaneous resolution of laryngomalacia and its symptoms

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ABSTRACT

*Introduction and objectives:* Laryngomalacia (LM) is the most common cause of congenital stridor. Tradition holds that the majority of patients resolve spontaneously by 12–18 months of age. The objective of this study was to systematically review the literature on the spontaneous resolution of LM and/or its presenting symptoms, in otherwise healthy infants.

*Methods:* Data sources included Medline/PubMed, EMBASE, Scopus, CINAHL, Proquest, Cochrane database, Cochrane Methodology Register, Web of Science Conference Proceedings Citation Index, and ACP Journal Club. Study inclusion criteria included participants with an endoscopic diagnosis of LM, and symptoms of stridor, swallowing dysfunction, and/or snoring/sleep-disordered breathing, that documented subjective or objective resolution endpoints. Surgical series, case reports, and narrative reviews were excluded. Studies with insufficient follow-up (<3 months), and patients with comorbidities without subgroup analysis were excluded. Two independent reviewers extracted follow-up duration, rate of retention, time to resolution of LM, and method of documentation of resolution.

*Results:* Of the 1146 articles identified, three met inclusion/exclusion criteria ($n$ = 411 patients). All were retrospective and used stridor resolution as the only endpoint. Resolution rate was 89%, with time to resolution ranging from 4 to 42 months. Level of evidence was low, and studies suffered from lack of follow-up, and no objective endpoints. Meta-analysis was not possible.

*Conclusions:* Endoscopic evidence of the natural history of laryngomalacia and its resolution is lacking. Low level of evidence supports that stridor and respiratory distress resolve, but the range of the time to resolution and rate of resolution is wide. Other clinical manifestations have not been studied. Prospective longitudinal trials are required to better understand the natural history.



## 1. Introduction

Congenital laryngomalacia (LM) is believed to be the most common cause of stridor in infants, and is estimated to cause 45–75% of cases of congenital stridor [1]. Although the disease was first described in 1897 [2], the term "laryngomalacia" was first proposed by Chevalier Jackson in 1942 [3]. It was designated to more accurately describe the concept of flaccid laryngeal tissue and prolapse of supraglottic structures on inspiration, which is not found in other sources of infantile stridor.

Classic symptoms of LM include inspiratory stridor and varying degrees of respiratory distress, which worsen with feeding, supine positioning and agitation. Frequently cited references claim these symptoms commonly manifest at birth, or after the first few weeks of life. The diagnosis is established by direct visualization of the larynx on endoscopy. Typical findings are prolapsing supra-arytenoid tissue during inspiration, shortening of the aryepiglottic folds and an "omega shaped" or retroflexed epiglottis, either alone or in combination [4].

There have been several LM classification schemes in the literature although none have been externally validated. Olney et al. classified LM into three types based on their site of supraglottic obstruction [4]. Type 1 LM involves prolapse of mucosa overlying the arytenoid cartilages. In type 2, there are foreshortened aryepiglottic folds. Posterior displacement of the epiglottis is type 3. This scheme has been adopted by most authors since the publication of this study.

The natural history of LM that has been described in the literature is one that worsens in the first four months of life,

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improves gradually between eight to twelve months, and almost universally resolves by 18 months [5]. The majority of patients are anticipated to resolve with expectant management, comprised of feeding modification and gastroesophageal reflux disease therapy, while 10% may require surgical intervention [6].

However, there is a growing body of recent literature suggesting that LM is a more complex and heterogeneous condition than previously thought. Some of these are case series that documented atypical primary presentations of LM, like snoring/sleep-disordered breathing (SDB), and swallowing dysfunction (SD) [7–9]. Other reports proposed some nomenclature that implied a different point in time for its onset ("late-onset" LM) [8,10], or a particular precipitating condition ("state-dependent" LM [11,12], or "occult" LM) [9]. In addition, a significant study has proposed a new pathophysiology for LM, namely abnormal sensorimotor integration [5]. With all this in mind, increasing reports of supraglottoplasty have concentrated on its efficacy to treat children with SDB, shifting the interest of the community to an end point not previously held as a primary one for LM [13].

Given this new evidence, a fresh look at the existing literature that shapes our understanding of LM is justified. We aimed to answer one of the most basic questions: what is the available level of evidence on its natural history?

The purpose of this work was to systematically appraise the available literature on the natural course of LM in an otherwise healthy newborn with no co-morbidities of neurological disease, or secondary airway lesions.

## 2. Methods

This review was conducted according to the standardized protocol, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [14].

In December 2014, an electronic search was performed by a specialized medical librarian (SC) using both controlled vocabulary (MESH and EMTREE) and text-words describing concepts of "laryngomalacia" and "time" or "watchful waiting." The search was applied to a variety of databases including Medline/PubMed (1946 to present), EMBASE (1974 to present), Scopus (1960 to present), CINAHL (1937 to present), Proquest Dissertations and Theses (1743 to present), Cochrane database of systematic reviews (2005 to present), Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Web of Science Conference Proceedings Citation Index (1990 to present), ACP Journal Club (1991 to present), and others. No limits were applied. The electronic search strategies and full list of databases are included in Appendix A. Reference lists of identified studies were scanned for additional studies.

Eligible studies were those that included neonates, infants, or children with a confirmed diagnosis of LM via flexible fiberoptic laryngeal endoscopy (FFLE) and/or rigid laryngoscopy/bronchoscopy (RLB). Participants must have had a documented history of one or more of the following classic or atypical presentations of LM:

a. Stridor with or without cyanosis/apparent life threatening events (ALTE), and/or
b. Swallowing dysfunction (SD) evaluated by history and clinical examination, fiberoptic endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallowing study (VFSS); and/or
c. Snoring/sleep disordered breathing (SDB) evaluated with structured history, overnight pulse oximetry (PO) or polysomnography (PSG).

Observational, descriptive, or interventional studies were eligible regardless of the primary outcome under study, so long as they included all patients presenting with LM, and provided information on natural (non-surgical) resolution, based on one or more of the following clearly stated endpoints (either subjective or objective):

(1) Symptoms of stridor/cyanosis, SDB, and/or SD; and/or
(2) Objective endpoints including FFLE/RLB, VFSS/FEES, and/or PO/PSG.

Types of studies that were excluded were purely surgical series, case reports, narrative reviews without original data, opinion articles, editorials, and cross-sectional or diagnostic studies without follow-up information on outcomes. Studies were also excluded if they included participants with neurological, cardiac, syndromic, or genetic conditions without a subgroup analysis. Those with insufficient follow-up information (less than three months), were also excluded.

Two independent authors (AI, HZ) reviewed all studies and classified them into folders based on type of study and reason for inclusion/exclusion. The articles that met the inclusion criteria for detailed review were analyzed by each author independently. Following that, agreement was reached by consensus on the articles to include in the final review, with any remaining disagreements adjudicated by a third author (HE).

The following data were extracted by two independent authors from each included study: author, journal, year of publication, study design, study duration, primary and secondary outcomes, sampling method, number of participants, methods of LM diagnosis, sub-type LM diagnoses, co-morbidities, presenting symptoms and signs, duration of follow-up, and rate of retention. Resolution rate of LM was collected, based on one or more of: endoscopic assessment, clinical assessment of stridor/respiratory distress, swallowing/VFSS/FEES, and SDB/PO/PSG. The mean, median, and range of time to each endpoint were also collected.

The quality and risk of bias of each included study was determined using the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses [15]. The case control scale or cohort scale was used depending on the type of study being assessed. This was again performed by two reviewers (AI, HZ), and any disagreements settled by consensus or by a third author (HE).

The data from each study was then summarized and descriptive statistics were performed to produce means and ranges of demographics and time to spontaneous resolution of LM, as well as the most common methods used for the assessment of resolution.

## 3. Results

The initial literature search identified 1922 citations. After removal of duplicates, 1146 articles remained. After reviewing the titles and abstracts, 919 were excluded due to irrelevance. 227 full articles were assessed for eligibility. Of these, 10 met the inclusion criteria and were eligible for inclusion in the systematic review. After detailed review of these 10 articles and application of exclusion criteria, only three satisfied all criteria and were included in the systematic review (Fig. 1).

A summary of the seven articles that met the inclusion criteria but were excluded after detailed review is in included in Table 1, including a summary of the design and reasons for exclusion. Three of the articles (McSwiney et al., Smith et al., and Friedman et al.) [16–18] consisted of retrospective questionnaires or telephone interviews of parents of patients with a previous diagnosis of LM. Aside from the methodological flaws associated with utilizing non-validated questionnaires retrospectively (many years after diagnosis), these articles lost 70–80% of their sample to follow-up or did not respond to the questionnaire.