



Diagnosis and management of type 1 laryngeal cleft: systematic review

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Background: Laryngeal cleft (LC) poses a diagnostic challenge due to its rarity and non-specific clinical features. There is poor consensus regarding management as either conservative or surgical management may be appropriate for type 1 LC, given the spectrum of disease patients present with. The objective was to review the current literature and propose diagnostic and management pathways for type 1 LC.

Methods: The study comprised a systematic review using data collected from PubMed, Medline and Cochrane library. A quality assessment of included studies was performed using a validated tool. A meta-analysis of proportions was performed for the outcome of each treatment modality using MedCalc software.

Results: Of 674 potential studies, 19 were included. Complete resolution rates of conservative management, injection augmentation and endoscopic surgery were 52.3% (95% CI, 32.3–71.9%), 69.2% (95% CI, 59.1–78.1%) and 65.4% (95% CI, 49.1–80.1%) respectively. There are research survey, diagnostic and treatment algorithms, and radiological investigations presented in the literature to assist in constructing an updated management algorithm.

Conclusions: We recommend that all patients receive initial 3-month trial of conservative therapy. Endoscopic surgery may be considered if conservative management fails or in the presence of other surgical indications. Injection augmentation may be performed prior to definitive surgical repair in selected patients who have comorbidities that increase aspiration risk to evaluate the potential effect of surgery.

Keywords: Pediatrics; laryngeal cleft (LC); radiologic swallowing assessment; bronchoscopy; conservative management; injection augmentation; endoscopic surgery

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Introduction

Laryngeal clefts (LC) are rare congenital/embryological abnormalities involving the larynx, trachea, and oesophagus (1). Many classifications have been devised by various authors (i.e., Armitage, Evans, Petterson), but the Benjamin and Inglis classification remains the most recognized (2-7). The diagnosis and management of type 1 LC remains controversial, with varying consensus across centres (1). This systematic review aims to provide guidance

in diagnosing and providing best-practice management for this condition.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (“PRISMA”) statement was followed in this review (8). PubMed, Medline and the Cochrane library were searched from 1984 to 28 July 2018. The

search was performed using the following combination of keywords: “laryngeal cleft”, “laryngotracheoesophageal cleft (LTEC)”, “cleft larynx”, “deep interarytenoid notch”, “laryngofissure”, “diagnostic criteria”, “symptoms”, “VFSS”, “videofluoroscopic swallowing study”, “swallow study”, “radiography”, “modified barium swallow”, “flexible nasendoscopy”, “flexible laryngoscopy”, “bronchoscopy”, “esophagoscopy”, “laryngoscopy”, “microlaryngoscopy”, “laryngotracheobronchoscopy”, “suspension laryngoscopy”, “management”, “treatment”, “conservative”, “surgery”, “endoscopic repair” and “injection”.

The inclusion criteria were: case reports, case series, research survey, retrospective analyses, clinical trials and randomized controlled trials that discussed diagnosis, treatment and treatment outcomes of type 1 LC in the pediatric population. Data were of children less than 18 years of age and comprised of articles available in full text only. Treatment modalities included were medical therapy, injection augmentation and endoscopic surgery. Studies were excluded if they discussed treatment modalities not mentioned, no diagnosis or management recommendations made where appropriate, patients with congenital syndromes or complex airway anomalies such as tracheoesophageal fistula.

Two reviewers screened titles and abstracts independently according to the predefined inclusion and exclusion criteria. The full texts of potentially relevant studies were examined subsequently. Disagreements between reviewers were resolved by discussion and examination of the full text. The following information was independently extracted by the reviewers: number of patients, study design, intervention, outcome and recommendation.

A quality assessment of included studies was also undertaken by the two reviewers using the National Institutes of Health Quality Assessment Tools (NIH-QAT) for Observational Cohort and Cross-Sectional Studies and Case Series Studies (9,10).

A meta-analysis of proportions was performed for the outcome of each treatment modality, reported as improvement or resolution of symptoms. MedCalc software for Windows was used for data analysis. The pooled proportion with 95% confidence interval (CI) is given to both the fixed effects model and random effects model used in this study. The type of model used was determined by the χ^2 test for heterogeneity. If a P value of <0.05 was obtained, the random effects model was used due to the presence of significant heterogeneity. The I^2 statistic was used to measure the degree of heterogeneity.

Results

A total of 1,040 studies were obtained following a combined search of electronic databases. Six hundred and seventy-four remained after removal of duplicates, of which 67 articles were selected for full text assessment after abstract screening. The final review identified a total of 19 articles for inclusion and data extraction. The PRISMA flow diagram for article inclusion is shown in *Figure 1*.

Amongst the 19 articles, there were 11 retrospective reviews, 1 prospective study, 5 case series, 1 case report and 1 research survey. The characteristics of these studies are demonstrated in *Table 1*.

Eleven out of 16 (68.8%) children with type 1 LC were identified via flexible bronchoscopy (FB) in a study by Boesch *et al.* (11), which was performed prior to confirmatory rigid laryngotracheobronchoscopy (LTB).

The pooled proportion of the conservative management group experiencing spontaneous symptom resolution and obtaining a normal diet for age across all included studies was 52.3% (95% CI, 32.3–71.9%). A random effects model was used to pool the proportion given significant heterogeneity seen across studies ($P=0.0263$, $Q=12.7$, $I^2=60.24\%$) (*Figure 2*). Forty-one patients who failed to improve with conservative therapy went on to have surgical repair. Sixty-six point five percent (95% CI, 41.7–87.1%) were reported with “symptom resolution”, “uncomplicated” or “good outcome”. The random effects model was used to pool the proportion given significant heterogeneity seen across studies ($P=0.110$, $Q=6.03$, $I^2=50.2\%$).

The pooled proportion of the injection augmentation group demonstrating complete resolution of either symptoms or abnormal modified barium swallow (MBS) findings was 69.2% (95% CI, 59.1–78.1%). A fixed effects model was used to pool proportion given no significant heterogeneity seen across studies ($P=0.980$, $Q=0.041$, $I^2=0\%$) (*Figure 3*).

The pooled proportion of the endoscopic surgery group which were reported as successful, defined as either improvement or complete resolution of symptoms or aspiration on swallowing assessment was 75.6% (95% CI, 69.2–81.3%). A fixed effects model was used to pool proportion given no significant heterogeneity seen across studies ($P=0.421$, $Q=9.18$, $I^2=1.93\%$). However, after excluding patients from Alexander *et al.* (12), Berzofsky *et al.* (13), and Ketcham *et al.*'s (14) studies which did not report outcomes of improvement and complete resolution separately, 65.4% (95% CI, 49.1–80.1%) were found to

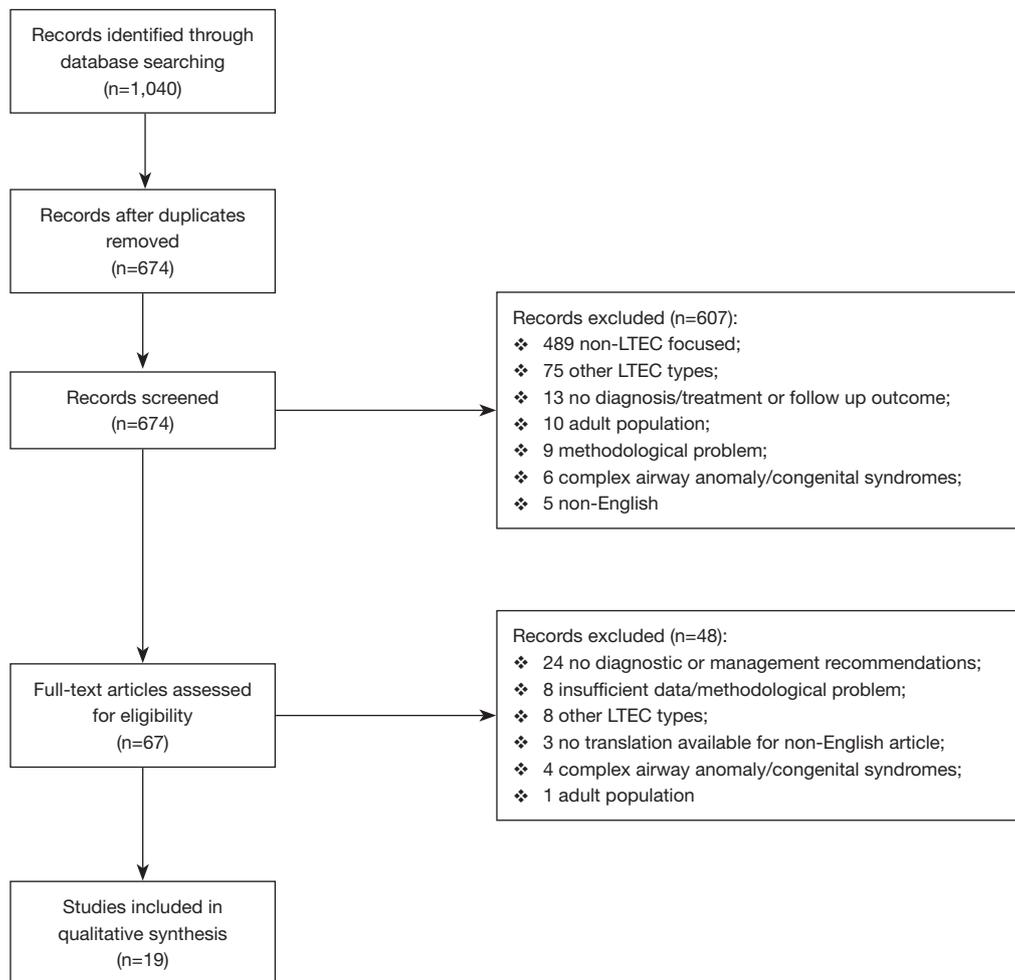


Figure 1 Data collection. LTEC, laryngotracheoesophageal cleft.

have complete resolution of symptoms or aspiration. The random effects model was used to pool proportion given significant heterogeneity seen across studies ($P=0.03$, $Q=13.9$, $I^2=56.9\%$) (Figure 4).

Quality assessment

The NIH-QAT for Observational Cohort and Cross-Sectional Studies and Case Series Studies were used to assess the quality of included studies (9,10). Tables 2 and 3 display the individual items of quality assessment for each paper along with the overall quality assessment score.

The NIH-QAT will allow for assessment of potential sources of bias, flaws in study methods, confounders and other relevant factors. A cumulative quality rating of “good”, “fair” or “poor” was given based on responses to the

questions. Generally, a good study has the least risk of bias and is considered valid. A fair study is prone to some bias but inadequate to invalidate its findings. A poor study has high risk of bias and is considered invalid. Any discrepancies between the two reviewers were resolved via discussion.

As the studies were mostly of retrospective nature, there was a lack of standardization for follow up periods. Additionally, patient outcomes were assessed differently—some clinically, and others radiographically [MBS, functional endoscopic evaluation of swallowing (FEES)], making it difficult for comparison of outcomes. The subjective nature of a clinical assessment also predisposed to bias. Lastly, the lack of blinding in all the included studies further added on to the possibility of bias. Nevertheless, many studies attempted to clarify potential confounders (such as difference in age and presence of comorbidities),

Table 1 Study characteristics

Study and type	Participant	Intervention	Outcome/recommendation
Berzofsky <i>et al.</i> , 2018—retrospective cohort study	35	Endoscopic surgery	<p>Patients with comorbidities affecting dysphagia had higher surgical success rates than the overall group</p> <p>Patients with comorbidities affecting dysphagia should not be excluded from consideration for surgical repair</p> <p>Dehydration and hematemesis were complications</p>
Yeung <i>et al.</i> , 2017—research survey/cross-sectional study	NA	NA	<p>Feeding therapy appropriate as initial management</p> <p>Anti-reflux therapy only when symptoms of laryngopharyngeal reflux present</p> <p>3–12 months trial of conservative therapy</p> <p>Post-operative swallowing evaluation at 4–8 weeks</p>
Boesch <i>et al.</i> , 2017—retrospective cohort study	96	Flexible bronchoscopy	Flexible bronchoscopist able to identify 11/16 (68.8%) of LC in which confirmatory rigid LTB was performed
Wentland <i>et al.</i> , 2016—retrospective cohort study	31	Endoscopic repair with post-operative MBS	<p>Children without comorbidities—clinical evaluation at 6 weeks post-operatively and MBS at 12 weeks</p> <p>Children with comorbidities—12 weeks post-operatively</p> <p>Children with silent aspiration/laryngeal penetration—MBS at 6 weeks</p>
Thottam <i>et al.</i> , 2016—retrospective cohort study	68	Injection augmentation	<p>Significant reduction of frank or silent aspiration</p> <p>Long-lasting effect in some</p> <p>Injection augmentation may be a more conservative option prior to surgical repair</p>
Strychosky <i>et al.</i> , 2016—retrospective cohort study	175	Pre- and post-operative MBS	<p>MBS study helps direct feeding therapy pre- and post-operatively</p> <p>Use of thickened feeds/repair alone may be successful if laryngeal penetration/aspiration present</p> <p>If oral or pharyngeal phase impairment present, swallowing dysfunction may persist despite surgical repair</p>
Fukumoto <i>et al.</i> , 2015—case series	5	Endoscopic surgery	<p>Laryngomalacia causing difficult extubation and laryngeal granuloma causing airway obstruction requiring repeat endoscopic surgery</p> <p>2.5 kg sufficient for endoscopic surgery</p>
Alexander <i>et al.</i> , 2015—retrospective cohort study	54	Endoscopic surgery	<p>Endoscopic surgery effective and safe</p> <p>Post-operative MBS at 8 weeks</p>
Rossi <i>et al.</i> , 2014—case report	1	Conservative management with thickened milk, anti-reflux medications and positioning techniques	Involvement of speech-language pathologist for earlier diagnosis and improved outcomes
Osborn <i>et al.</i> , 2014—retrospective cohort study	60	Post-operative swallowing evaluation (MBS/FEES)	Post-operative MBS/FEES at 3, 6, 12 and 24 months

Table 1 (*continued*)

Table 1 (continued)

Study and type	Participant	Intervention	Outcome/recommendation
Ojha <i>et al.</i> , 2014—retrospective cohort study	42	Conservative treatment with thickened feeds, anti-reflux therapy and positional techniques	At least 3 months conservative therapy
		Surgical intervention after failed conservative management	Surgical repair should be conducted in children with comorbidities increasing aspiration risk
			Post-operative MBS at 6 weeks, continue thickened feeds if no improvement
			Repeat MBS at 3 monthly intervals until resolution
			Referral to appropriate specialist if no sign of improvement after 6 months
Mangat <i>et al.</i> , 2012—case series	18	Injection augmentation	Post-operative laryngeal swelling occurred as complication Some patients do not require further intervention as they develop protective swallowing strategies
Cohen <i>et al.</i> , 2011—case series	10	Injection augmentation	Endoscopic surgery if initial resolution but relapse of clinical symptoms
Bakthavachalam <i>et al.</i> , 2010—retrospective cohort study	59	Conservative management with thickened feeds	Trial of conservative therapy up to 2 years old
		Endoscopic surgery	Consider surgical intervention after 2 years old
Ketcham <i>et al.</i> , 2008—case series	16	Endoscopic surgery	No statistically significant difference in success in patients with or without comorbidities Cleft dehiscence occurred as a complication
Rahbar <i>et al.</i> , 2006—retrospective cohort study	2	Conservative management with thickened feeds Surgical intervention with failed conservative therapy	Gastroesophageal reflux disease must be controlled with medical/surgical therapy prior to cleft repair
Chien <i>et al.</i> , 2006—prospective cohort study	20	Careful history and physical examination Rigid LTB to confirm diagnosis	All patients should receive trial of conservative prior to consideration of surgical intervention
Boseley <i>et al.</i> , 2006—case series	3	Conservative management with thickened feeds	Good outcomes with both conservative and surgical treatment
		Endoscopic surgery	
Watters <i>et al.</i> , 2003—retrospective cohort study	12	Conservative management with anti-reflux therapy and thickened feeds	Minimum 4 months trial of conservative therapy before surgical intervention

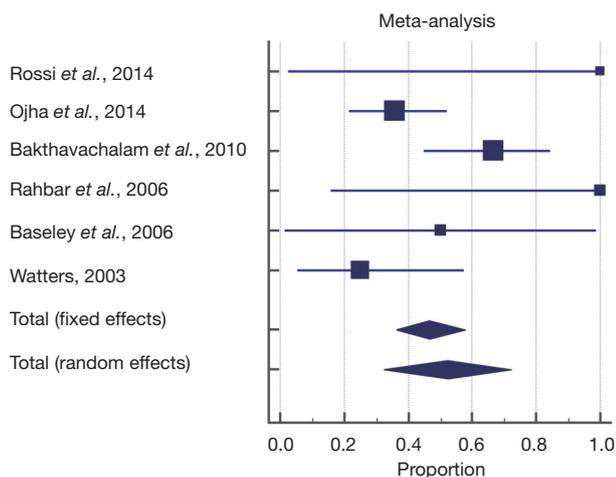


Figure 2 Proportion meta-analysis of conservative management group with symptom resolution.

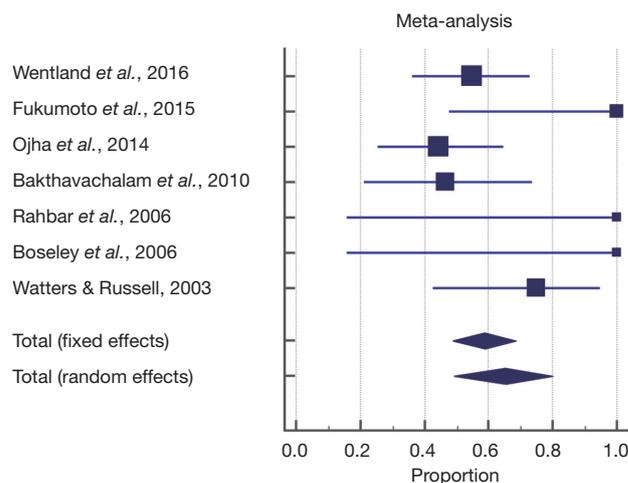


Figure 4 Proportion meta-analysis of endoscopic surgery group with symptom resolution.

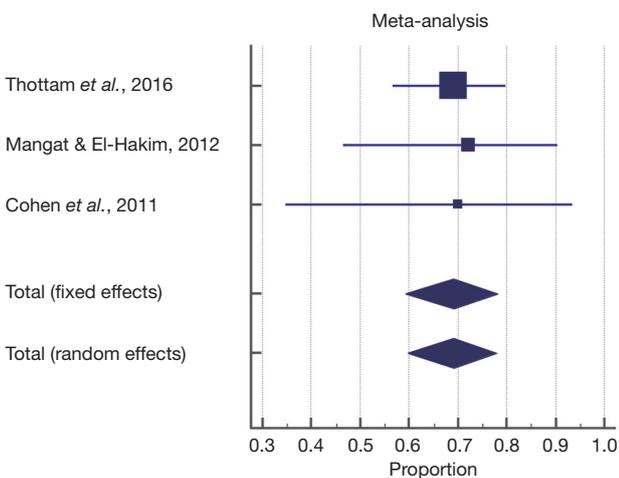


Figure 3 Proportion meta-analysis of injection augmentation group with symptom resolution.

with some providing statistical analyses on their significance (12,13,15-20). The majority of studies also provided a clear description of results and outcomes.

Most of the papers were thought to be of “fair” quality except for two articles which were considered “good”. Given the undistinguished studies included, this review may not necessarily provide the most accurate assessment of evidence-based medicine with regards to managing pediatric laryngeal cleft.

Discussion

Incidence

Incidence rates have increased over the years—6.2% to 7.6% in recent years, as compared to 0.1% to 0.47% in initial reports (21-23).

Such a significant increase in incidence rates reported can be attributed to greater awareness and understanding of the disease, higher levels of suspicion, along with the availability of more advanced diagnostic tools (21,24).

Data regarding the exact epidemiology of the laryngeal cleft types remains unavailable, likely due to the rarity of laryngeal clefts. Some recent studies suggest that type 1 LC is the most commonly diagnosed (16,25,26). Other studies had varying data which indicated a more even spread amongst the different types (27,28). This variance amongst the studies could possibly be due to a particular focus on surgical management, which is the mainstay treatment of LC types 3 and 4. Additionally, there is a potentially undiagnosed population of type 1 LC because these clefts can be asymptomatic and remain clinically silent.

Comorbidities and associations

Majority of laryngeal clefts occur sporadically, although autosomal dominant traits have been observed in some families (29). Additionally, substance abuse, premature

Table 2 Quality assessment—observational cohort and cross-sectional studies

Studies	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Berzofsky <i>et al.</i> , 2018	Y	Y	Y	N	N	Y	N	NA	Y	NA	Y	N	Y	Y	Fair
Yeung <i>et al.</i> , 2017—research survey	Y	Y	CD	Y	NA	NA	NA	NA	NA	NA	Y	N	NA	NA	Fair; wide involvement of experts internationally from 7 different countries, consensus was defined when majority (>80%) agreed
Boesch <i>et al.</i> , 2017	Y	Y	Y	Y	N	Y	NA	Y	Y	NA	Y	N	NA	N	Fair
Wentland <i>et al.</i> , 2016	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Thottam <i>et al.</i> , 2016	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Strychowsky <i>et al.</i> , 2016	Y	N	Y	N	N	Y	Y	Y	Y	N	Y	N	Y	Y	Fair
Alexander <i>et al.</i> , 2015	Y	Y	Y	Y	N	Y	CD	NA	N	NA	N	N	Y	Y	Fair
Osborn <i>et al.</i> , 2014	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Ojha <i>et al.</i> , 2014	Y	Y	Y	Y	N	Y	Y	NA	N	Y	Y	N	Y	Y	Fair
Bakthavachalam <i>et al.</i> , 2010	Y	Y	Y	Y	N	Y	CD	NA	N	N	N	N	Y	Y	Fair
Rahbar <i>et al.</i> , 2006	Y	Y	Y	Y	N	Y	Y	NA	N	N	N	N	Y	N	Fair
Chien <i>et al.</i> , 2006	Y	Y	Y	Y	N	Y	CD	NA	Y	N	Y	N	Y	N	Fair
Watters <i>et al.</i> , 2003	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	N	Fair

Y, yes; N, no; NA, not applicable; CD, cannot determine.

Table 3 Quality assessment—case series studies

Studies	1	2	3	4	5	6	7	8	9	Quality
Fukumoto <i>et al.</i> , 2015	N	Y	Y	Y	Y	N	Y	NA	Y	Fair
Rossi <i>et al.</i> , 2014	Y	Y	NA	NA	Y	Y	Y	NA	Y	Fair
Mangat <i>et al.</i> , 2012	Y	Y	Y	CD	Y	Y	Y	NA	Y	Fair
Cohen <i>et al.</i> , 2011	Y	Y	Y	Y	Y	Y	CD	Y	Y	Fair
Ketcham <i>et al.</i> , 2008	Y	Y	Y	Y	Y	Y	CD	Y	Y	Good
Boseley <i>et al.</i> , 2006	Y	Y	N	Y	Y	Y	Y	NA	Y	Fair

Y, yes; N, no; NA, not applicable; CD, cannot determine.

delivery, and polyhydramnios are well-recognized maternal risk factors (23,29).

Gastroesophageal reflux is a common association seen with posterior laryngeal cleft, with a reported incidence

ranging from 21% to 44%. It may potentially aggravate existing pulmonary conditions and lead to failure of laryngeal cleft repair. Hence it has been advised to be evaluated and controlled prior to surgical repair. Medical

therapy with acid suppression medication and/or surgical intervention may be used to manage affected cases (23,27).

Other known associated anomalies include esophageal atresia (20% to 37%) with or without tracheoesophageal fistula, tracheal or subglottic stenosis, and laryngo-tracheobronchomalacia (5,24,30,31). These anomalies can largely be excluded via an endoscopic examination (24). Neuromuscular disorders are commonly seen in patients with laryngeal clefts, with an overall incidence of 13.6% reported (32).

Additionally, genetic syndromes such as Opitz-Friaz syndrome, Pallister-Hall syndrome, DiGeorge syndrome, CHARGE syndrome, and VACTERL association are also known to be frequently associated with laryngeal clefts (33).

There are contrasting opinions regarding the impact of associated comorbidities on prognosis. de Alarcón *et al.* (34) demonstrated that the presence of additional airway anomalies did not impact overall success rate of laryngeal cleft surgery. Other authors noted otherwise, with significantly worse outcomes in terms of conservative and surgical success seen in patients with comorbidities conferring increased aspiration risk (15,17). A more severe clinical course has been seen in patients with concomitant laryngomalacia and type 1 LC despite laryngomalacia being a relatively benign clinical condition (35). Additional management steps in view of such associated anomalies have also been suggested, i.e., individualized postoperative pulmonary plans in those with laryngeal cleft and concomitant subglottic stenosis or laryngomalacia, and a complete evaluation of the airway during a tracheoesophageal fistula repair to exclude the presence of a laryngeal cleft (34,36).

Clinical features

Clinical manifestations of laryngeal clefts appear to correlate with the severity or type of cleft (24). Less severe clefts can be asymptomatic, and some may remain clinically silent (18,24). Some type 1 LC may also be diagnosed incidentally while undergoing an endoscopic evaluation for other reasons (19).

Mild to moderate symptoms typically manifest in type 1 LC, some of which include stridor, hoarse cries, and mild feeding difficulties (24,37). Other presentations such as aspiration, recurrent pulmonary infections and cyanosis during feeding may also occur (24,38). Additionally, respiratory consequences are usually negligible (24).

On the contrary, type 3 and 4 LCs tend to be associated

with more severe pulmonary involvement, i.e., recurrent pneumonia and pulmonary mucous production (37). Type 4 LCs may also present with early onset respiratory distress requiring mechanical ventilation, which is associated with poor prognosis (24).

A review by Leboulanger *et al.* (24) found that common clinical symptoms of laryngeal clefts, in order of frequency are:

- ❖ Swallowing disorders, i.e., aspiration and cyanosis during feeding, chronic cough;
- ❖ Pharyngeal and laryngeal symptoms, i.e., stridor, toneless cry, pharyngeal hypersecretions;
- ❖ Respiratory symptoms, i.e., recurrent pneumonia, respiratory distress at birth.

Type 1 LCs are generally difficult to diagnose and require a high level of suspicion given the inconsistent and non-specific clinical features (38). Subsequent management is also complicated by the fact that type 1 LC can be considered for either conservative or surgical management. Therefore, it is of paramount importance to tailor treatment according to an individual's spectrum of disease (37). Undeniably, the overall approach to diagnosing and managing type 1 LC constitutes difficult clinical decisions which this paper aims to inform and streamline.

Diagnosis

Rigid LTB

Evaluation with rigid LTB, along with palpation of the interarytenoid space remains the gold standard for diagnosing an LC (1,37,39,40). Spontaneous breathing during general anesthesia reduces the likelihood of missing tracheobronchial dyskinesia or a tracheobronchial laryngomalacia (24).

During endoscopy, the length of the LC is classified using the Benjamin and Inglis endoscopic staging system (41). Additionally, a complete assessment of the respiratory tract is recommended given the relatively high association of LCs with tracheobronchial fistulas, reportedly 10% to 60% (24).

Other pre-operative investigations such as videofluoroscopy, chest x-ray and barium swallow may potentially miss a small type 1 LC (39).

Nonetheless, it remains a challenge to distinguish a child with persistent respiratory symptoms or feeding problems secondary to other disorders, such as laryngomalacia, gastroesophageal reflux disease, birth trauma and congenital infections, from one with a laryngeal cleft. Hence, posing a difficulty of identifying the patient who requires a rigid

LTB (37). Therefore, apart from potential clues such as the persistence of symptoms despite aggressive management, a high degree of suspicion is essential (37,38).

Radiological assessment chest computed tomography (CT)/chest X-rays

Routine chest X-rays are typically inconclusive, although there may be signs of parenchymal changes in association with aspiration (24). A study by Williams *et al.* (42) did not find any statistically significant correlation between the type of LC and the radiological changes observed on chest X-rays and CT scans.

Although radiographic imaging provides little diagnostic value, potential benefits still exist when used selectively in patients with possible associated lung abnormalities. Management was altered in 43.8% of Williams *et al.*'s (42) patient population based on additional information from CT findings. Further, MRI scans may be useful for assessing associated malformations despite the lack of diagnostic value (24).

FB

During an FB, which may be performed as a procedure in an outpatient clinic under local anesthesia, a jaw thrust maneuver is performed while the lower edge of the bronchoscope tip is used to probe the interarytenoid space (11,17). The larynx may be concurrently examined for laryngomalacia, direct aspiration, and assessed for laryngeal mobility and sensitivity (24).

However, FB alone cannot rule out presence of an LC. This is because an LC may be inadvertently overlooked due to the poor visualization of the posterior glottic space, as a result of redundant mucosa between the esophagus and trachea apposing each other and prolapsing into the cleft (23,24, 41).

A retrospective review by Boesch *et al.* (11) evaluated the overall diagnostic yield of FB for wheezing children. Eleven out of 16 (68.8%) children with type 1 LC were identified via FB, which was performed prior to confirmatory rigid LTB. This further emphasizes that rigid LTB remains the gold standard for diagnosis, as type 1 LC may be missed on FB despite careful evaluation by experienced bronchoscopists.

MBS & FEES

MBS (or videofluoroscopic swallowing studies) and FEES can both diagnose laryngeal penetration or aspiration (1).

MBS is a non-invasive test, albeit with inferior laryngeal anatomical visualization compared to FEES (22). Observation of deep penetration with certain dietary consistencies may predict aspiration with trial of thinner consistencies. Therefore, a more viscous consistency is introduced to the feeding regimen without further testing, to avoid additional radiation and barium aspiration (13,17). Even so, some patients with normal MBS findings were found to have respiratory symptoms that were severe enough to warrant surgical intervention, indicating that MBS findings may not correlate with symptomatology (16,43,44).

On the other hand, FEES provides direct visualization of the larynx, and allows assessment of vocal cord mobility, extent of pooling and penetration, along with localizing the site of aspiration (22). It also allows assessment of the position of spillage, i.e., lateral or anterior to posterior spillage, which may indicate an alternative cause of aspiration. Lateral spillage over the aryepiglottic folds results in suspicion of neurological aspiration, making diagnosis of laryngeal cleft less likely (17).

Boseley *et al.* (39) advocated the use of FEES as a diagnostic tool to establish aspiration patterns in children suspicious for type 1 LC, as well as to assist in management decisions. Although children under 1 year old can undergo FEES, there may be difficulties performing it due to the lack of cooperation and patient intolerance (22,28). Distress during the examination will affect the accuracy of the swallow assessment as crying can result in aspiration as they try to swallow simultaneously. Hence, children between the age of 3 to 12 months and over the age of 4 may be better suited for FEES (22).

The findings of MBS or FEES may be useful in guiding management. In select cases, i.e., those without comorbidities, the presence of a symptomatic cleft may be inferred when persistent interarytenoid penetration is present. Conservative management may then be initiated without the need for confirmation with LTB and its associated anesthetic risk (1). Management with thickened feeds or surgical repair of the cleft alone may be successful if laryngeal penetration/aspiration is present. However, if oral/pharyngeal phase is impaired or there is delayed triggering of swallow, persistent swallowing dysfunction may occur despite rigorous surgical repair (16).

Nonetheless, it is important to note that false negative results on MBS or FEES may occur with intermittent aspiration, and hence normal results from either test do not exclude the presence of a laryngeal cleft (22,37,45). Given

the possibility of alternative diagnoses and mechanisms of aspiration, careful evaluation of MBS and FEES results is warranted prior to consideration for surgical repair (22).

Prognosis

The prognosis of LC is related to the type of cleft, associated comorbidities, and the respiratory status of the patient (24,45). Mortality rates of 42% in type 1 LC, and 46% for LCs in general have been reported in the past (45-47). In comparison to the 6% to 25% mortality rates in more recent reports, this drastic reduction in mortality can be attributed to earlier diagnosis and advancements in management (24).

Different rates of success have been reported for all forms of treatment. With conservative management, failure rates ranged from 45% to 80%, with variable length of trial (15,22,23,37,48). Failure was defined as persistence of symptoms. Regarding injection augmentation, complete resolution of symptoms was reported in 39.7% to 72% of patients (20,44,49). Surgical management seemed to indicate relatively high rates of success, ranging from 73% to 100% (12,22,23,27,48,50,51). The definition of success differed between studies, they include return to normal feeding, improvement of aspiration severity and symptom resolution (15,19,40).

Treatment

Conservative management

Conservative management encompasses management of associated comorbidities (i.e., gastroesophageal reflux disease, food allergy, eosinophilic esophagitis, reactive airway disease), as well as feeding therapy (1,6). Medical management of associated comorbidities aims to improve disorders that may contribute to the swallowing impairments. On the other hand, feeding therapy involves modification to feed thickness, feeding adjuncts, positional strategies and maneuvers to prevent aspiration (6,15,19,22,33). In a research survey by Yeung *et al.* (1), the majority of clinicians recommended anti-reflux therapy only in the presence of laryngopharyngeal reflux symptoms.

Patients with severe symptoms or complications of aspiration, e.g., recurrent pneumonia, may benefit from nasogastric tube feeding or gastrostomy (23,24). Nissen fundoplication should also be considered in patients with a history of gastroesophageal reflux (23,27).

The recommended duration of conservative therapy was variable amongst different authors, ranging from 1 to 12 months (1,15,22,23,37). Most patients who failed to improve with conservative therapy proceeded to have surgical intervention.

One hundred and three patients who underwent conservative therapy have been identified from seven relevant studies, 20 of whom were asymptomatic and had type 1 LC diagnosed incidentally while undergoing endoscopy for other reasons (15,19,22,23,27,33,39). Fifty-two point three percent (95% CI, 32.3–71.9%) experienced spontaneous symptom resolution, obtaining a normal diet for age, with conservative management. Forty-one patients who failed to improve with conservative therapy went on to have surgical repair. Sixty-six point five percent (95% CI, 41.7–87.1%) were reported with “symptom resolution”, “uncomplicated” or “good outcome”. It is reassuring to see modest surgical success rates despite failing a trial of conservative therapy. This suggests that conservative therapy may be appropriate as initial management (1,22).

Bakthavachalam *et al.* (19) have found a direct correlation between the age at diagnosis and age at resolution of aspiration in patients treated conservatively. Patients who were diagnosed after 2 years old were found to have resolution of aspiration at a significantly older age with conservative treatment. Interestingly, the age of surgical repair had no statistically significant impact on the age of resolution of aspiration until past the age of 2.

With these findings, it is recommended that patients can be managed medically up to the age of 2 years, in the absence of indications for definitive surgical repair, as mentioned later (19). Following that, surgical intervention should be considered if symptoms fail to resolve, in order to prevent permanent lung damage and its associated morbidity (23). An initial 3-month trial of conservative management with thickened feeds and positional strategies appears reasonable. Anti-reflux medication should also be administered if laryngopharyngeal reflux symptoms are present. Subsequently, a multidisciplinary team review should be conducted to determine if there is clinical improvement of symptoms. If persistent symptoms are present, there may be consideration of either endoscopic repair or injection augmentation.

Injection augmentation

Injection augmentation refers to a minimally invasive technique involving the injection of a biologic material

into the interarytenoid space submucosally, increasing bulk in the region (52). It is usually consented for in conjunction with an initial endoscopy following a trial of conservative management, to avoid a second anesthetic where possible (49). As discussed previously, injection augmentation is useful in patients with concurrent comorbidities to determine if they are responsible for the patient's symptoms.

Some clinicians may choose to conduct a trial of injection augmentation to evaluate the potential effect of a surgical repair, which is highly effective but invasive (1,44). In cases complicated by concurrent neurologic or airway anomalies, injection augmentation is useful in determining whether the laryngeal cleft or other anomalies are responsible for their symptoms (53). Benefits of injection augmentation include its short procedural time, reversibility and being less invasive than surgical repair. However, there are also associated risks such as filler migration, regional scarring, along with a possible need for repeat procedures (1).

Majority of patients, 69.2% (95% CI, 59.1–78.1%), demonstrated complete resolution of either symptoms or abnormal MBS findings. Once again, it is important to note that MBS findings do not necessarily correlate with symptom improvement (22). Injection augmentation has also been shown to provide statistically significant improvement in those with frank or silent aspiration, proven on MBS or FEES. Patients with penetration on thin liquids were found to have higher odds of successful injection augmentation. Contrastingly, those with silent aspiration had decreased odds of success. There was no difference in the odds of success for those with frank aspiration (20).

Postoperative laryngeal swelling was seen in a patient with signs of obstruction resolving within 48 hours of systemic steroids and observation (49). Injection augmentation appeared relatively safe with the remaining patients having uncomplicated procedures.

A high success rate of 90% to 100% in patients who subsequently underwent surgical repair was reported (20,44). This may possibly reflect the ability of injection augmentation to identify patients who are likely to respond favorably to formal surgical repair. Endoscopic repair is thus recommended in patients with initial resolution but with relapse of clinical symptoms (44).

The duration of symptom resolution or improvement corresponds to the half-life of the injected material (i.e., lasting days with gelfoam and months with hyaluronic acid) (49). Cohen *et al.* (44) observed that some patients seemed to benefit from injection augmentation for longer

than expected periods. Thirty-nine out of 68 (57.4%) patients in Thottam *et al.*'s (20) retrospective review experienced a long-lasting effect and did not require further surgical repair. Thus, it suggests that injection augmentation may be definitive treatment in some patients, who will not require further intervention (49). A possible explanation is scarring and improved competence of the deficient interarytenoid space due to an inflammatory response produced by the injected agent (44,53). Another explanation may be the development of compensatory swallowing strategies during the period of glottal competence before the effect of the injection augmentation wears out (44,49).

Ten patients required repeat injections as the relapses coincided with the lapse of the injected material's half-life. Of which, nine patients experienced consistent positive response. No information was provided for the remaining patient (20,49). It is important to note that all patients who underwent repeat injections in Thottam *et al.*'s (20) study later required formal surgical repair. This suggests that patients with relapse of symptoms are unlikely to have permanent resolution of symptoms with repeat injections, despite being a favorable candidate for surgical repair. Unfortunately, there was insufficient data to determine the success rate with a single injection. There was also no data suggesting when post-operative swallowing evaluation should be performed and after what length of time with symptom resolution, would injection augmentation be considered to have been a definitive treatment.

The follow-up period of patients who received injection augmentation ranged from 0.4 to 29 months. Two patients had unknown length of follow-up. Given the short follow-up period in some patients, perhaps if followed further, some would be seen to have return of symptoms.

Endoscopic surgery

Surgical repair of a type 1 LC was first reported in 1955 (4). Currently, there are a number of endoscopic techniques utilized in surgically managing a laryngeal cleft—including microflap approximation and suture techniques with or without laser assistance (21).

Indications for surgical repair include (1,15,21):

- ❖ Severe symptoms;
- ❖ Lack of/poor response to conservative management (i.e., medical management, feeding therapy);
- ❖ Deteriorating pulmonary function;
- ❖ Presence of other comorbidities which may contribute to aspiration risk;

- ❖ Objective findings on upper aerodigestive investigation/imaging (i.e., persistence of aspiration on MBS).

Fukumoto *et al.* (50) mentioned that 2.5 kg may be sufficient for endoscopic surgery as the lowest body weight was a 1-month old infant weighing 2,460 g at surgery. However, in a research survey by Yeung *et al.* (1), most members (65%, 13/20) did not use minimum weight as a criterion for assessing patient suitability for surgery.

Endoscopic approaches have notably high efficacy and safety for Type 1 LC repairs (54). Increased success rates were also observed with the avoidance of intubation, allowing for spontaneous breathing and enhanced exposure under general anesthesia (27).

Seventy-five point six percent (95% CI, 69.2–81.3%) of the endoscopic surgical procedures performed were successful, defined as either improvement or complete resolution of symptoms or aspiration on swallowing assessment. However, after excluding patients from Alexander *et al.* (12), Berzofsky *et al.* (13), and Ketcham *et al.*'s studies (14) which did not report outcomes of improvement and complete resolution separately, only 65.4% (95% CI, 49.1–80.1%) were found to have complete resolution of symptoms or aspiration. The significant failure rate may indicate that other associated anomalies may be responsible for their symptoms. This suggests that it may be worthwhile performing a trial of injection augmentation prior to definitive surgery to evaluate its potential effects. Nevertheless, Ojha *et al.* (15) recommend that surgical repair should still be conducted in children who have comorbidities that increase aspiration risk even though they may be unlikely to have complete resolution of symptoms. They believe that the benefit of providing some symptomatic relief outweighs the risks of surgery. Similarly, Berzofsky *et al.* (13) stated that such patients should not be excluded from consideration of surgical repair, with their findings of higher surgical success rates in patients with comorbidities affecting dysphagia than the overall group. Ketcham *et al.*'s study (14) also reported no statistically significant difference in success rates in patients with or without comorbidities.

The complications seen include a case of laryngeal granuloma causing airway obstruction, cleft dehiscence and hematemesis, two cases of laryngomalacia requiring repeat endoscopic surgery and four cases of dehydration (13,14,50).

Post-operative swallowing evaluation

There has been no consensus as to the appropriate timing

for post-operative swallowing evaluation, i.e., MBS or FEES, after surgical repair of LCs (17).

MBS is recommended to be performed 6 to 8 weeks after surgery to allow time for post-operative supraglottic edema to resolve (12,15). Patients should remain on a thickened feeding regimen if they show no signs of improvement. They should then be re-evaluated at 3, 6, 12 and 24 months if swallowing problems persist (15,17,18). Majority who regained a normal diet with minor modifications did so within the first 3 months after surgery. Therefore, it is unlikely for children to recover normal swallowing after 24 months. The decision to cease swallowing evaluation in a child who persistently aspirates after cleft repair should be based on clinical judgement (18). Ojha *et al.* (15) have suggested that a second rigid LTB or a neurology referral should be made if studies still demonstrate aspiration at 6 months.

Based on literature review, authors proposed management pathways for otolaryngologists to differentiate type 1 LC from other otolaryngologic conditions (*Figure 5*). The authors recognise the limitations of these recommendations given that the available studies on the topic are of lacking quality.

Conclusions

We recommend a diagnostic and treatment algorithm which may be considered in patients with suspected type 1 LC. All patients should have an initial 3-month trial of conservative management with thickened feeds and positional strategies. Anti-reflux therapy should be provided to patients with symptoms of laryngopharyngeal reflux. Endoscopic surgical repair should be performed in the presence of indications, i.e., severe symptoms, deteriorating pulmonary function, poor response to conservative management, persistence of aspiration on MBS or presence of other comorbidities which may contribute to aspiration risk. Prior to definitive repair, injection augmentation may be performed in selected patients with concurrent comorbidities to evaluate the potential effect of surgical repair. MBS should be performed at 6 to 8 weeks post-operatively and re-evaluated at 3, 6, 12 and 24 months if swallowing problems persist. Patients should remain on thickened feeding regimen if they show no signs of improvement. Consider repeating rigid LTB or referral to the appropriate specialist, i.e., neurologist, if there are no signs of improvement by 6 months.

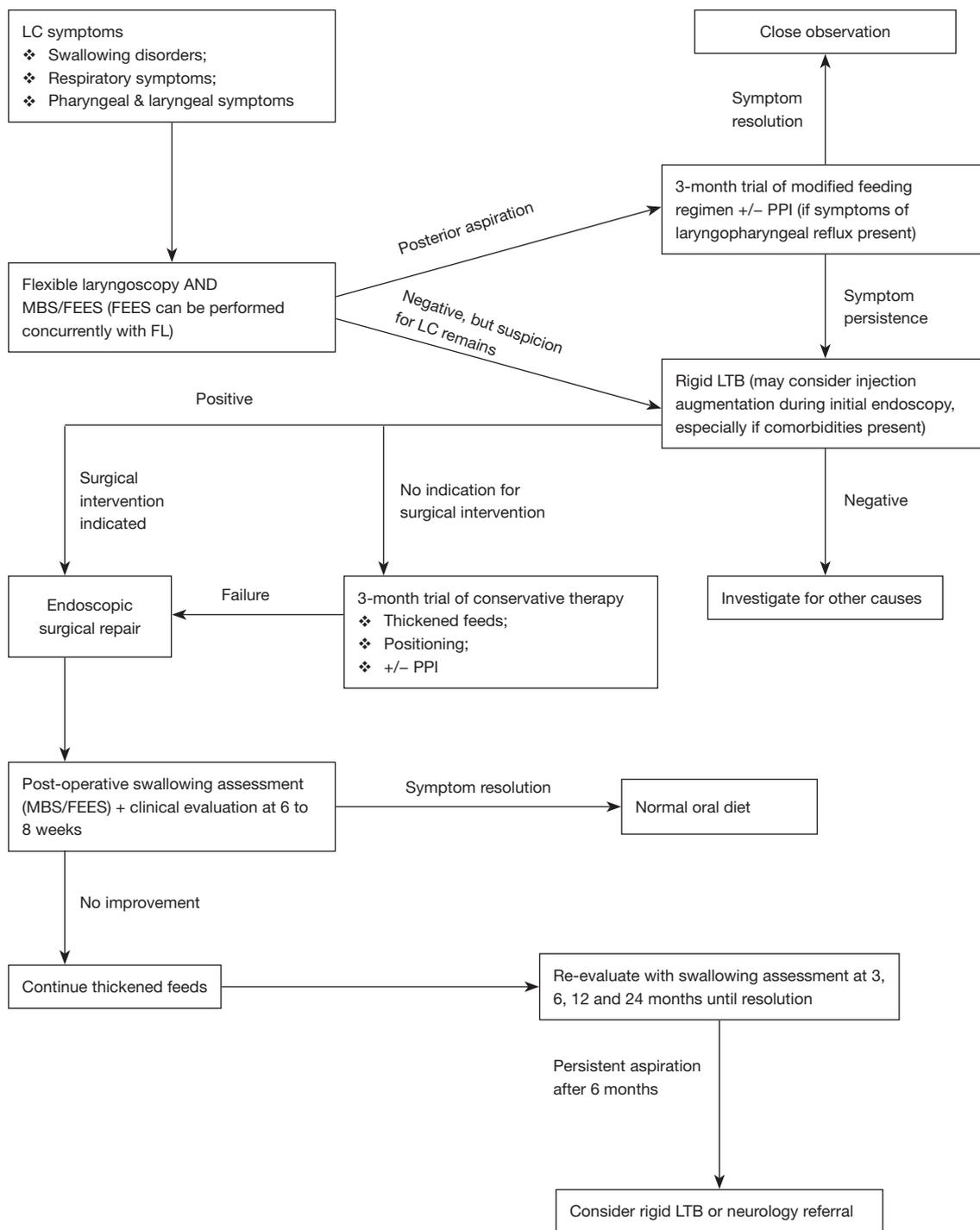


Figure 5 Proposed management pathway for suspected type 1 laryngeal cleft. PPI, proton-pump inhibitor; MBS, modified barium swallow; FEES, functional endoscopic evaluation of swallowing; FL, flexible laryngoscopy; LC, laryngeal cleft; LTB, laryngotracheobronchoscopy.

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Footnote

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