AIRWAY SURGERY IN CHILDREN

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AIRWAY SURGERY IN CHILDREN

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EDITORIAL
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Editorial: Airway Surgery in Children

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Editorial on the Research Topic

Airway Surgery in Children

Airway surgery in children is a challenging field, requiring highly competent and organized surgeons and airway teams. An increasing number of pediatric airway teams have been established all over the world. The article "*Teamwork in Airway Surgery*" reported by Elliott et al. describes the principles, obstacles, and solutions that inspired one of the first and busiest airway teams in the world (based in London). Acknowledging the local history, the theory and mindset behind the conception of a tracheal team, how to deal with practical and ideological difficulties, and future perspectives, is very inspiring for anyone who is dedicating efforts to the care of pediatric airway patients. Our recently published (1) experience is quite similar and has been directly inspired by the London tracheal team.

The first approach to the patient with airway symptoms through endoscopic evaluation is in most cases crucial to define an early and precise diagnosis. "*Pharyngomalacia in neonates: the missed issue*" by Moslehi et al. describes a condition often misdiagnosed, causing noisy breathing or more severe symptoms, and provides useful information on how to perform precise endoscopic evaluation, establishing the severity of the condition, and offering possible treatment options. It is an interesting manuscript as it addresses an unacknowledged and probably underdiagnosed cause of airway obstruction in neonates, problems for differential diagnosis, and choices of treatment.

In "*Endoscopic, preoperative assessment, classification of stenosis, decision-making*" the authors underline the importance of a step-by-step rigorous endoscopic evaluation, including various practical maneuvers and tips that lead to a precise classification of the stenosis and consequently the most appropriate treatment options (Filauro et al.). Among the available classifications, the authors propose the new European Laryngeal Classification (2), which is a useful instrument to tailor the best treatment modality for each patient. In our opinion, the value of a well-conducted pre-operative endoscopic evaluation cannot be overestimated and is the first step to providing the correct surgical approach and outcome.

The most important message of "*Ongoing laryngeal stenosis: conservative management and alternatives to tracheostomy*" by Schweiger and Manica is to emphasize that a proactive endoscopic treatment is effective in most cases of ongoing laryngeal stenosis, avoiding tracheostomy in the majority of patients. While in the past most of the patients who could not be weaned off ventilation through an endotracheal tube were submitted to a tracheostomy. In recent years, with proper repeated endoscopic treatment and follow-up, a tracheostomy should be considered only as the last resort. However, the best treatment modality (balloon vs. bougies) and the role of adjuvant treatments (steroids, mitomycin, topic ointments, pump inhibitors) have still to be determined. It is also important to recognize that dilatation can be repeated, but if the patient requires more than 3 or 4 dilatations another treatment option should be considered.

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In "*Surgical management of anterior glottic webs*," Kuo and Rutter provide an article with great technical detail and useful illustrations, describing how to treat laryngeal webs, which are rare congenital anomalies often associated with 22q11.2 deletions, encompassing different degrees of severity, and requiring different approaches. The less experienced and confident readers with these challenging patients will take advantage of the large experience of the Cincinnati Airway team, described in this manuscript.

The treatment of bilateral vocal cord palsy remains a very controversial issue. Trozzi et al. in "*Surgical options for pediatric vocal cord palsy: state of the art*" present a comprehensive review of the literature describing several surgical techniques proposed over the last decades and underline the importance of pursuing, if possible, two main goals or principles: avoiding tracheostomy and being very conservative when it comes to preserving voice quality both avoiding permanent scarring to the vocal cords and/or oversizing the posterior glottis. These concepts are especially valuable for our pediatric patients.

Another very controversial and challenging topic is recurrent papillomatosis. The manuscript "*Airway Papillomatosis: new treatments for an old challenge*" by Kumar and Preciado provides new insights on innovative approaches as novel instrumentation for endoscopic removal of papillomas or even alternatives to it. Among the novel adjuvant therapies described, systemic bevacizumab is a promising treatment that could probably represent an alternative to the surgery itself. In particular, there are reports on the efficacy of systemic bevacizumab in treating aggressive papillomatosis not responsive to other treatments. The potential appeal is enhanced by the fact that bevacizumab seems to be more effective on tracheobronchial localizations, which are more difficult to treat and surgically assess and tend to significantly impact patients' morbidity and mortality. Prospective studies in larger series using standardized protocols and long follow-up have to be conducted to validate and make this new treatment option more widespread.

Kamran and Jennings in "*Tracheomalacia and tracheobronchomalacia in Pediatrics: an overview of evaluation, medical management, and surgical treatment*" present a comprehensive description of the anatomy, clinical symptoms, medical, and surgical treatment of tracheobronchomalacia, a challenging condition, often under- or misdiagnosed in pediatrics. The global approach to these patients includes a three phase bronchoscopic evaluation and a dynamic angio CT scan to study airway/vascular conflicts. The surgical treatment should be individualized. Particularly in those patients, presenting intrusion of the posterior wall of the trachea, posterior tracheobronchopexy, recently described by Boston group (3), which seems to be a better option than the classical approach through an aortopexy (4). As for other airway conditions, a multidisciplinary approach, taking into account feeding and breathing patterns and associated symptoms both during the day and during sleep that may impact a child's general growth and development, is the only way to offer the best treatment for the individual patient affected with tracheomalacia.

The last four papers of this issue describe clinical cases. In "*The important role of endoscopy in management of pediatric pseudomembranous necrotizing tracheitis,*" the authors propose the use of flexible endoscopy in children presenting acute onset of respiratory obstruction (Wu X. et al.). Although in this condition tracheal fragility could be a contraindication to endoscopy, the authors present a favorable outcome in two patients, in which the procedure provided an early diagnosis and consequently prompted mechanical debridement.

The importance of endoscopy, associated with CT scan, for differential diagnosis in an infant presenting with wheezing, is stressed by the group of Cutrera, who in "*Recurrent wheezing in pre-school age: not only airway reactivity!*" presented a case of the surgical removal of a mediastinal bronchogenic cyst (Roversi et al.). In our experience, there are a wide range of pathologies that must be considered and that have been diagnosed in children treated for a long time for bronchial hyper-reactivity or asthma, both primary conditions such as tumors, malacia, congenital laryngotracheal stenosis, and secondary vascular or mass compression. The message of this report is that the threshold for more invasive investigation as endoscopy and CT scan should not be too high in symptomatic and not responding patients.

Primary tracheobronchial tumors in children are rare, and surgery is the only therapeutic tool in many cases (5), for which open or endoscopic approaches can be appropriate options. In the case presented by Wu L. et al. ("*Case Report: Resection of Giant Endotracheal Hamartoma by Electrosurgical Snaring via Fi beroptic Bronchoscopy in a 9-Year-Old Boy*") a tracheal hamartoma was successfully removed endoscopically using interventional bronchoscopy. The authors wisely reinforce the importance of a multidisciplinary approach to the patient, for whom different surgical approaches had been discussed. Another example of a multidisciplinary approach is described by Bing et al., who wrote "*Congenital Bronchobiliary Fistula: A Case Report and Literature Review*". A rare congenital fistula was diagnosed through fistulography performed during a bronchoscopy and successfully removed thoracoscopically. In these rare anomalies of the airway, such as the one presented here, bronchography associated with bronchoscopy can still play an important role, as demonstrated in the literature and our experience (6–8).

In conclusion, "Airway surgery in children" comprehends various congenital and acquired airway conditions, some more others less common, but all of them represent significant challenges for the airway teams. The present issue provides many important messages that can be summarized in the use of a multidisciplinary approach with rigorous and rational diagnostic work-up to establish prompt and appropriate treatment tailored to each patient by an experienced surgeon open to innovative approaches and using age appropriate tools for young patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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REVIEW
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Airway Papillomatosis: New Treatments for an Old Challenge

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Recurrent respiratory papillomatosis (RRP) is the recurrent growth of small, benign tumors, or papillomas, in the respiratory tract, caused by human papillomavirus (HPV). Currently, there is no cure. Palliative treatments seek to prevent airway obstruction, keep underlying tissues healthy, and maintain voice quality. The most common intervention, the local surgical removal of papillomas, may be inadequate as a standalone treatment for pediatric populations that experience rapid papilloma regrowth, as repeated surgeries cause increased damage to the surrounding tissues and impose significant emotional and economic burden on families. Interferon α and Cidofovir have been shown to lengthen the time between surgical interventions and/or decrease the total number of procedures needed, although the evidence of their efficacy and safety is controversial. Novel therapies, including photodynamic therapy, indole-3-carbinol, anti-reflux medication, heat shock protein, and Mumps and HPV vaccination, may provide potential avenues for treatment, but require further research. Among all the novel therapies investigated, systemic bevacizumab seems to offer the most promising alternative to surgery. Randomized control trials to investigate its impact, especially in a pediatric population, should be conducted before implementing it as a standard form of care. This review will summarize the latest literature on medical care for aggressive RRP disease.

Keywords: RRP, bevacizumab, HPV vaccine, cidofovir, interferon-α, indole-3-carbinol

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INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a chronic disease caused by human papillomavirus (HPV), usually types 6 and 11. The lesions of RRP most frequently appear in the larynx (**Figure 1**), but may also emerge in the mouth, trachea, bronchia, lung parenchyma, and esophagus. The juvenile-onset form of RRP, in which symptoms present before 12 years, is more aggressive than the adult-onset form, and symptoms are more severe. Papilloma recurrence is especially rapid in children under 3 years, who experience shorter intervals between surgical interventions and thus more surgeries overall. The likelihood of the infection spreading beyond the larynx and incidence of a tracheostomy, to help keep the trachea open are also greater in this population (1). Patients with juvenile onset RRP undergo on average 20 surgical interventions, most of which are in childhood (2).

The traditional surgical method for surgical extirpation classically involved KTP (potassium titanyl phosphate) or carbon dioxide lasers (3). Given the potentially severe side effects of laser ablation, including respiratory tract burns and laryngeal scarring, microdebriders have become an increasingly popular surgical tool, particularly among pediatric otolaryngologists, for bulky disease (3). This hand-held device can remove the diseased tissue more precisely, reducing damage

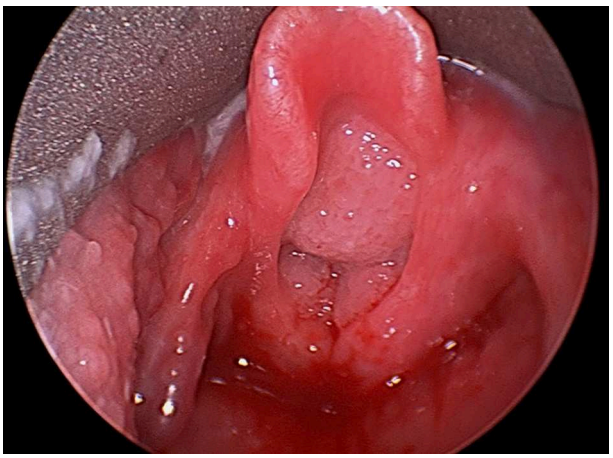

FIGURE 1 | Direct laryngoscopic image of large bulky airway papillomatosis obstructing the laryngeal inlet.

to surrounding tissues (3). However, given the aggressive nature of juvenile RRP, debridements are still frequent, and over time, still wear down the underlying tissue significantly, with high incidence of scar formation. As such, several medical therapies have been investigated to improve the outcome of surgery, by increasing the length of time between operations, or by minimizing recurrence of RRP lesions.

INTERFERON α

Interferon α, a protein produced by leucocytes in reaction to diverse stimuli, including viral infection, was one of the first potential medical treatments studied (4). Its value as an adjuvant treatment is controversial. In a large study of 85 children and 84 adults, 58% of children ended the year-long treatment period of intramuscular interferon α injections three times a week without evidence of RRP (5). The frequency of papilloma recurrence decreased in 74% of all children treated (5). In a randomized control trial of 123 patients under 21 however, the slowed growth rate of papillomas in the experimental group that received interferon α intramuscular injections was not sustained over the course of the year-long treatment (6). Similarly another study found that, 20 years after the conclusion of treatment with interferon α, only 42% of patients indicated a long term response, and all those who relapsed had the juvenile onset form of RRP (7). Most studies investigating interferon α have also reported serious side effects, like neurologic disorders, leukopenia, and thrombocytopenia (5). For these reasons, its use by pediatric otolaryngologists has dwindled and is generally not recommended (1). In 2014, only 4% of children with RRP received interferon α as adjuvant therapy (1).

CIDOFOVIR

This broad-spectrum, antiviral drug that inhibits viral DNA polymerases has been shown to be promising as an adjuvant intralesional therapy to surgery for RRP. Intralesional cidofovir injections are the most commonly administered medical treatment for RRP among pediatric otolaryngologists (1). All papers published between 1998 and 2011 that investigated the efficacy of intralesional cidofovir reported at least one instance of disease remission (8). However, since most of these studies are uncontrolled case studies, it is unclear whether the benefits are caused by Cidofovir, or are part of the natural course of the disease. A randomized control trial found that there were no statistically significant differences in papilloma severity or Health-Related Quality of Life between a control group, treated with surgical interventions as needed and intralesional injections of saline, and the experimental group, treated with surgery and intralesional Cidofovir, after 12 months of treatment (9). Both groups experienced a significant decrease in the severity of the disease over the course of the year, indicating that the disease may regress over time on its own (9). Another review that looked at 27 studies of Cidofovir administration, all published before 2011, found that the average complete remission rate with cidofovir was 37% in pediatric studies (10). There have also been some severe side-effects associated with cidofovir, as a review found that 1.7 and 1% of 447 RRP patients experienced malignant transformation and nephrotoxicity, respectively (8). Other side effects include cutaneous rash, headache, and vocal cord scarring (11). Given these potential complications and the lack of an accepted protocol for dosage or frequency of administration, this drug is not a reliable adjuvant (4).

Cidofovir has also been administered as a systemic rather than local treatment for RRP cases that are complicated by lung disease. Four single case studies have shown that intravenous cidofovir led to disease remission, which is not the normal progression of the disease with lung involvement (11). All these studies employed hyperhydration and probenecid, a uric acid reducer, to reduce the chances of nephrotoxicity (11). Only one patient experienced side-effects, partial alopecia and leukopenia, from a combination therapy of cidofovir and interferon (12). The doses of both drugs were reduced in response. Eighteen months after the end of treatment, the patient had only required surgery for RRP once, and her lung disease had stabilized (12).

A novel method of Cidofovir delivery is inhalation. Few studies have investigated the efficacy of this method, but it may be promising for patients who have not responded to other forms of treatment, like a 4-month-old boy who, despite biweekly microdebridements and intralesional Cidofovir and intravenous interferon α injections, experienced worsening symptoms (13). Within 6 weeks of 40 mg of nebulized Cidofovir daily, 12 days on and 2 days off, the time between debridements increased (13). Six months later, the patient did not show any symptoms (13). To summarize, although Cidofovir in various administration forms remains widely used, its treatment results at best are mixed, and its potential for side effects are somewhat limiting.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) involves introducing a light sensitive substance, called a photo-sensitizer, orally or by injection, into diseased tissue and activating the substance

with laser light to induce necrosis. One of the major benefits of PDT is the ability to destroy tumors without affecting surrounding tissue (4). Case studies have shown significantly slower rates of papilloma regrowth soon after PDT, administered as an adjuvant or standalone therapy, and in some cases, the absence of disease after several weeks (14, 15). There have been only a few randomized control trials to investigate the impact of PDT, but the most recent found that the disease recurred after 3–5 years, likely because it generates its impact through a short-term immune response (16). Further research should be conducted to ascertain its efficacy and safety.

INDOLE-3-CARBINOL

Found in high concentrations in cruciferous vegetables like broccoli and cabbage, indole-3-carbinol modifies estrogen metabolism to alter cellular proliferation and DNA synthesis. The most recent clinical trial found that, after taking indole-3-carbinol twice a day, with a 200 mg dose for adults and weight-determined doses for children, for an average of 50.2 months, 70% of subjects experienced either a complete or partial response (17). Of the pediatric patients, one experienced a complete response, three a partial response, and five no response at all (17). It is unclear why adult patients responded better to indole-3-carbinol than pediatric patients. The less aggressive nature of adult-onset RRP may be a factor. Given the unpromising results in the pediatric population, there has not been much more research on treating juvenile onset RRP with of indole-3-carbinol.

CELECOXIB

Celecoxib is an anti-inflammatory drug that inhibits cyclooxygenase-2 (COX-2), an enzyme that leads to inflammation and pain, and is commonly used to treat arthritis. *In-vitro* studies have shown that papilloma cells overexpress COX-2 as a result of enhanced Epidermal growth factor receptor (EGFR) signaling, and that this activity is important to their growth (18). A combination therapy of celecoxib and erlotinib, a EGFR kinase inhibitor, helped control progressive RRP in a 58-year-old man a by slowing papilloma growth, rendering further surgery unnecessary (19). An ongoing randomized control trial sponsored by Northwell Health aims to determine whether celecoxib can decrease the rate of recurrence of papillomas in both adult and pediatric patients (4).

ANTI-REFLUX MEDICATION

Case studies have shown that treating gastroesophageal reflux disease (GERD) with anti- reflux medication in patients with juvenile-onset RRP can help slow the rate of papilloma regrowth (20, 21). In one study, patients who failed to comply with GERD treatment experienced recurrence (20). A retrospective chart review also showed that pediatric patients treated for RRP who were not treated for reflux were significantly more likely to develop laryngeal webs after the surgical removal of papillomas (22). While there is inconclusive evidence that GERD aggravates RRP, managing it makes sense for patients who have clinical presentation of GERD and complicated, progressive cases of RRP (23).

HEAT SHOCK PROTEIN

Among the 700 children with RRP managed by 74 pediatric otolaryngologists, who were surveyed on their use of adjuvant treatment, 11 patients received HSP-E7, a recombinant fusion protein comprised of heat shock protein 65 (Hsp65) and the E7 protein of HPV type 16 (1). HSP-E7 has been investigated as a treatment in several diseases that stem from HPV, including genital warts and intraepithelial neoplasia (24). Evidence suggests that it may be reactive against more HPV strains than just HPV 16 (24). In an open-label trial of 27 pediatric RRP patients, the median interval between surgeries following treatment of HSP-E7 was significantly prolonged compared to the pre-treatment median (24). There were few complications, only mild-to-moderate injection site reactions. While there are no ongoing clinical trials to investigate the efficacy of Hsp-E7, it is a promising treatment.

HPV VACCINE

A few case reports and studies have documented the use of the HPV vaccine as an adjuvant therapy. There are currently three approved HPV vaccines: the bivalent Cervarix, tetravalent Gardasil, and nonavalent Gardasil 9. The tetravalent vaccine acts targets HPV-6, HPV-11, HPV-16, HPV-18. A recent systematic review and meta-analysis found that the mean duration between surgeries in 63 juvenile and adult RRP patients significantly increased after HPV vaccination, from 7 to 34 months on average (25). The study found no significant differences by age of RRP onset (25). Other case studies not included in the meta-analysis have also shown Gardasil's efficacy in pediatric patients, as it increases the time between surgeries significantly or in some cases, causes complete remission (26, 27).

Intramuscular HPV vaccination might be more efficacious than previously identified, more common treatments like intralesional cidofovir. A retrospective case study that followed juvenile and adult-onset RRP patients for 22 years found that only two of the 13 patients treated with surgery and Gardasil relapsed, whereas all control patients, treated with surgery and Cidofovir, experienced papilloma regrowth (28). The average length of time to disease recurrence was also significantly longer in treated patients than controls (28).

One of the most promising aspects of HPV as adjuvant therapy is that it does not have any severe side effects. Additionally, with increasing vaccination rates, the incidence of juvenile RRP may decrease overall, as this form of the disease is commonly acquired when a baby is exposed to genital warts caused by the HPV 6 or 11 virus during childbirth (4).

MUMPS VACCINE

There have been very few studies on the efficacy of the mumps vaccine as an adjuvant therapy, although current research is promising. A case study found that remission was induced in nine of 11 pediatric patients treated with intralesional injections of the vaccine at 3- to 12-week intervals along with laser surgery (29). A retrospective study comparing Cidofovir and the measles, mumps, and rubella (MMR) vaccine as adjuvant therapies in a pediatric population found that there were no significant differences between those children treated with intralesional cidofovir and MMR injections after debridements (30).

BEVACIZUMAB

Bevacizumab is human monoclonal antibody that binds to and prevents the interaction of vascular endothelial growth factor (VEGF) with receptors. VEGF activity has a role in RRP development, as *in vitro* studies have shown strong expression of VEGF-A in papilloma epithelium and the expression of VEGFR-1 and VEGFR-2 messenger RNAs in underlying vascular endothelial cells (31).

The first studies looking at bevacizumab as a treatment for RRP investigated the benefit of intralesional injections as an adjuvant therapy to surgery. A study of three patients between 3 and 6 years-of-age with severe RRP (i.e., with at least four procedures per year) found that all patients experienced increased time between surgical debridement and pulsed KTP laser treatments and less severe RRP several weeks after the termination of bevacizumab treatment compared to before (32). They also showed improved voice-related quality of life (32).

Aside from case reports, case control studies have also been conducted to investigate the efficacy of bevacizumab as adjuvant therapy. After 532 nm KTP laser treatment followed by sublesional bevacizumab injections in the more diseased vocal fold, and saline injections in the other fold, 16 of the 20 adult patients with bilateral vocal fold RRP had fewer papilloma in the treated fold, as determined by endoscopic imaging (33). Three of the 20 patients had no disease in either fold, and none of the patients experienced any complications from the treatment (33).

Based on these promising results, a larger study looking at the efficacy of bevacizumab was conducted in a pediatric population. In 10 children between 18 months and 18 years with progressive, non-responsive RRP, three intralesional bevacizumab injections of 2.5 mg/ml 2–3 weeks apart, along with laser therapy, increased the median length of time between surgical procedures, decreased the median number of procedures per year, and improved voice-related quality of life (3). One of the limitations of the study is that the dosing is an estimation based on doses in pediatric ophthalmology. The amount injected into paillomas was also not the same for every patient, as it varied based on severity of disease.

Some studies have tried to determine optimal dosages. Another study looking at nine pediatric patients with juvenile onset RRP also found that, after a series of five subepithelial injections administered at 4–6 week intervals, with a mean dose of 14.25 mg, together with KTP laser ablation, all nine patients (with a median age of 8 years) experienced increased time interval between injections (34). These results indicate that showed that high-dose bevacizumab treatment does not have any complications and may be highly effective.

Following evidence that showed the efficacy of intralesional bevacizumab, research turned to address systemic bevacizumab, that is an especially promising treatment for patients with complex diagnoses. The first report of intravenous administration showed that, with a median of 6 courses in doses of 5, 10, 15 mg/kg, all treated patients with progressive RRP showed papilloma regression (35). The patients included four cases of adult onset RRP and one juvenile onset. The five patients collectively underwent 18 surgical interventions the year before bevacizumab, but only the adult case required surgery after treatment because of a malignant transformation the following year (35).

Other single case reports have corroborated the efficacy of systemic bevacizumab without finding complications, although most of these are in adult patients. In a 42 year old man with severe tracheal RRP, a low dose of 5 mg/kg, increased to 10 mg/kg of bevacizumab over time, helped achieve disease regression 3 months after treatment cessation (36). A 12-month follow-up revealed the patient remained disease free. Six courses of systemic bevacizumab treatment of 5 mg/kg every 2 weeks for a 87-year-old patient who had not responded to intralesional cidofovir, an endobronchial stent, or HPV vaccination, also helped achieve a significant decrease in the mass of the lobe and a patent bronchus (37). After two courses of 10 mg/kg intravenous injections every 2 weeks, a 63-year-old with severe RRP showed less lung involvement and no evidence of tracheal obstruction (37).

The only published case report in children is of a 12-year-old female with progressive laryngotracheal papillomatosis and lung involvement who, after 3 months of initiating systemic bevacizumab treatment, showed a partial response in the larynx and an almost complete response in the trachea (38). After 5 months, the patient no longer showed lung involvement. These results are even more impressive given that, over a 10-year span, the patient had been initiated on Gardasil, interferon, celecoxib, anti-reflux medication, zithromycin, and propranolol, and not responded to any (38).

Systemic bevacizumab's potential as treatment for the most aggressive forms of RRP is best summarized by the results of an electronic survey of the RRP Task Force of the American Society of Pediatric Otolaryngology, American Broncho-Esophagological Association, and physicians who have treated RRP with systemic bevacizumab (39). The 11 completed surveys obtained from nine medical centers showed that most of the patients treated with bevacizumab had a long history of juvenile onset RRP and had failed to show sustained responses to cidofovir, interferon, and celecoxib. Physicians gave treatment in the range of 5–10 mg/kg per dose. Seven of the eight patients treated had a partial response and one showed a complete response to treatment (39). All patients experienced increased time between surgeries, now on the order of months. In three of the four patients with lung involvement, three showed the improvement or resolution of pulmonary papilloma and one showed the stabilization of the disease. Only two patients experienced minor complications, hemoptysis, and proteinuria.

To ascertain the causal effect of bevacizumab, determine appropriate doses, and identify any potential complications, randomized control trials and larger case control studies must be conducted. Moreover, protocols to define duration of treatment, while controlling for any potential rebound effects need to be elaborated.

CONCLUSIONS

Although an optimal, universally effective medical adjuvant therapy for RRP has not been yet found, promising results from RRP vaccination as a therapeutic approach along with the usage of systemic bevacizumab offer hope for improved outcomes for these children in the coming years. Optimal protocols for treatment should be developed in the near future.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Tracheomalacia and Tracheobronchomalacia in Pediatrics: An Overview of Evaluation, Medical Management, and Surgical Treatment

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Tracheobronchomalacia (TBM) refers to airway collapse due to typically excessive posterior membrane intrusion and often associated with anterior cartilage compression. TBM occurs either in isolation or in association with other congenital or acquired conditions. Patients with TM typically present non-specific respiratory symptoms, ranging from noisy breathing with a typical barking cough to respiratory distress episodes to acute life-threatening events and recurrent and/or prolonged respiratory infections. There are no definitive standardized guidelines for the evaluation, diagnosis, and treatment of TBM; therefore, patients may be initially misdiagnosed and incorrectly treated. Although milder cases of TBM may become asymptomatic as the diameter of the airway enlarges with the child, in cases of severe TBM, more aggressive management is warranted. This article is an overview of the clinical presentation, evaluation, diagnosis, medical management, and surgical treatment options in pediatric tracheomalacia.

Keywords: tracheomalacia, tracheobronchomalacia, aortopexy, tracheopexy, tracheobronchopexy

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INTRODUCTION

Tracheomalacia (TM) refers to an excessive increase in compliance of the trachea, such that the airway is more susceptible to dynamic and/or static collapse; this is distinguishable from intrinsic airway stenosis caused by mural problems such as complete tracheal rings. TM may be localized or generalized. The mainstem bronchi may also be affected, which is referred to as tracheobronchomalacia (TBM). Less commonly, the mainstem bronchi and/or their distal divisions at the lobar or segmental level are affected alone, which is known as bronchomalacia (BM) (1–5).

The causes of airway malacia can be broadly divided into those congenital conditions that are associated with an excessively compliant or collapsible airway and those where the airway cartilage is found to be normal but is malformed due to a secondary or acquired cause. Tracheomalacia is the most common congenital tracheal abnormality with a reported incidence of 1 in 2,100 children (6), which is likely an underestimation given a wide spectrum of non-specific symptoms that are initially misdiagnosed (7). Primary or congenital TM/TBM can be found alone or in conjunction with other genetic and congenital disorders (5, 8, 9). Given the common origin of the trachea and esophagus during embryologic development, TM/TBM is a common respiratory problem in children who have esophageal atresia with or without tracheal-esophageal fistula (EA/TEF) (10–14). TM/TBM may also be associated with other airway and lung pathologies, such as laryngomalacia, laryngeal

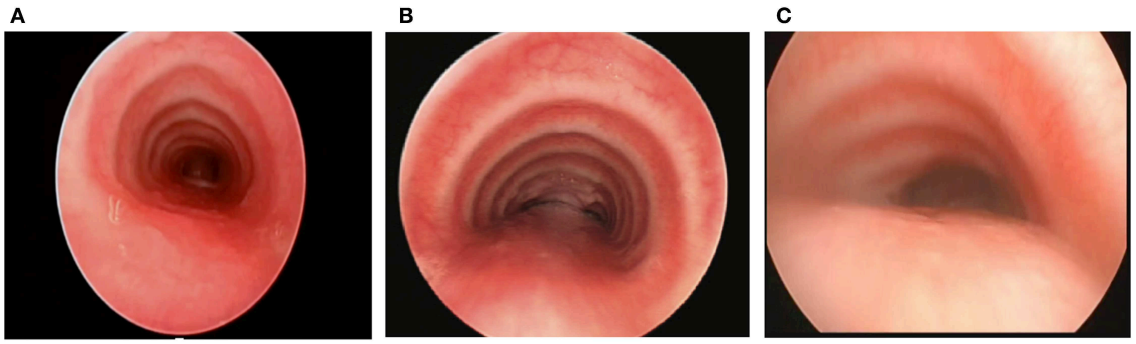

FIGURE 1 | (A) Tracheal structure with normal C-shape rings. **(B)** U-shaped rings with a wider posterior membrane, demonstrating posterior intrusion. **(C)** Bow-shaped rings with a broad posterior membrane and severe posterior intrusion.

clefts, bronchopulmonary dysplasia, or cystic fibrosis (7, 15, 16). The airway malacia can be acquired from cartilage malformation caused by external compression from vascular abnormalities, such as vascular ring, pulmonary sling, or aberrant subclavian artery, or other mediastinal masses (17–20). Prolonged intubation, chronic infections, or inflammatory conditions may also cause TM/TBM (21–23).

ANATOMY

The normal trachea and main bronchi are supported by relatively rigid C-shaped cartilages anteriorly and laterally, and a short pliable posterior membrane (5). Changes in pressure, in part, determine the airway diameter during the respiratory cycle. The pliable posterior membrane moves inward during expiration, narrowing the airway and accelerating the airflow and mucus clearance. In a healthy person, the decrease in airway diameter is negligible and typically not more than 10–20% even with coughing, although some adult studies have shown up to 50% posterior intrusion with coughing by airway imaging and CT scans (24, 25). In patients with TM/TBM, the physiological narrowing of the airway is accentuated during expiration, and in severe cases, a clinically obvious airway collapse occurs predominantly when the expiratory effort is increased, such as during coughing or crying. The airway collapse may be attributable to the dynamic posterior intrusion and/or combined with a region of fixed anterior collapse. If the entire cartilage ring configures in an upside-down U shape or even bow shape, the posterior membrane is broader and more dynamic and intrudes into the airway lumen during expiration and periods of increased intra-thoracic pressure (**Figure 1**) (14). Also, intrinsic weakness of cartilages can have a profound effect on airway compliance; in the worst cases resulting in severe airway collapse at rest or with minimal exhalation effort. Anterior compression is typically caused by blood vessels such as the aorta or innominate artery, which may alter the shape of the cartilages even if they have normal strength leading to fixed anterior airway collapse.

SYMPTOMS AND SIGNS

Clinical presentation of TM/TBM includes a range of non-specific respiratory symptoms, depending on the location, extent, and severity of the airway collapse. Many children with TM/TBM do not show symptoms until age 2–3 months (5, 26, 27). However, in cases with long-segment TM/TBM, symptoms may begin at birth (27). In some patients, TM/TBM becomes apparent soon after repair of EA/TEF when they cannot be extubated (27). A barking cough with expiratory rhonchi or inspiratory stridor may be present in most patients with TM/TBM. The extensive airway collapse can lead to ineffective cough and reduced clearance of secretions. As a result, patients with TM/TBM are at increased risk of frequent upper respiratory infections, prolonged recovery from an upper respiratory infection, and recurrent or persistent pneumonia (24, 28–31). Also, the airway obstruction often results in insufficient ventilation; therefore, patients may experience exercise intolerance, hypoxic episodes, or apneic events (5, 6, 27, 28). The symptoms can be worsened by any activities or conditions that increase the intrathoracic pressure and the patient's respiratory efforts, including activities such as coughing, crying, Valsalva maneuvers, feeding, forced expiration, or lying supine (5, 27).

DIAGNOSIS AND EVALUATION

There is no definitive standardized guideline for diagnosis and evaluation of TM/TBM. The diagnosis should be suspected by a clinical history of signs and symptoms that would be suggestive of TM/TBM, including barky cough, noisy breathing, recurrent pneumonia, prolonged pulmonary infection, feeding difficulties with dyspnea, cough, and aspiration, transient respiratory distress requiring positive pressure, oxygen dependence, ventilator dependence, blue spells, and apparent life-threatening events (ALTEs) (27, 28). Patients with apneic events require careful cardiac and neurologic evaluations to exclude these causes. Esophageal abnormalities, including strictures and tracheoesophageal fistulas, as well as gastroesophageal reflux, must be ruled out (27).

For the most accurate diagnosis of TM/TBM, direct visualization is achieved through flexible and rigid endoscopy, including laryngoscopy, tracheoscopy, and bronchoscopy (13, 24, 30, 31). Three-phase dynamic bronchoscopy is considered the gold standard for the diagnosis of TM/TBM. The first phase occurs while the patient is shallow breathing, which reveals the basic anatomy of the airway as well as compression, cartilage malformation, and secretion accumulation. It may also show vocal cord motion, depending on the depth of anesthesia. Vocal cord motion may be altered and even markedly depressed, sometimes differently on each vocal cord, with small amounts of anesthesia; this must be taken into consideration during the exam (13). The second phase is to induce coughing and Valsalva maneuvers while observing the entire airway, which reveals the maximum dynamic airway collapse as well as the secretion accumulation that gets displaced from the distal airways and comes into the larger airways. This phase is critical for identifying TM/TBM. The third phase is to distend the airways to 40–60 cm of water after aspirating all secretions out, which reveals the structures and lesions that may not normally be seen. This phase allows the identification of tracheoesophageal fistula (TEF), tracheal diverticulum, and aberrant bronchi (29) as well as regions of fixed compression. There are no standard criteria for establishing the diagnosis of TM/TBM endoscopically; however, most surgeons consider a more than 50% dynamic narrowing in the airway lumen with forced exhalation or coughing to diagnose TM/TBM (27). The majority of children with symptomatic TM/TBM have more than 75% airway collapse of one or more

A

	FOE awake	Shallow breathing	Cough valsalva	Sedated distended pressure?	Contrast study
Tonsils					
Epiglottis		NL			
AE folds		NL			
Arytenoids		NL			
Cords		POST SCAR			
L. cleft		REPAIRED			
Subglottis		10% ELLIP			
T1		"U" 10% POST	30%	FLAT	
T2		"BOW" 10% R	20%	FLAT	
T3		"BOW" 10% L	10%	FLAT	
Carina		"BOW"		FLAT	
L1		"U" 40% R	60% R	40% R	
L2		"U"	30% POST		
L3		"U"	10% POST		
R1		"U"	10%		
R2		"U"	10%		
BI		"U"	10%		
Tracheal diverticulum?		POSTERIOR CARINA		5mm DEEP	NO
TEF?					NO
Posterior artery?		NO		NO	
Secretions		THICK			
Other					
Notes			SCABBARD LMB		

B

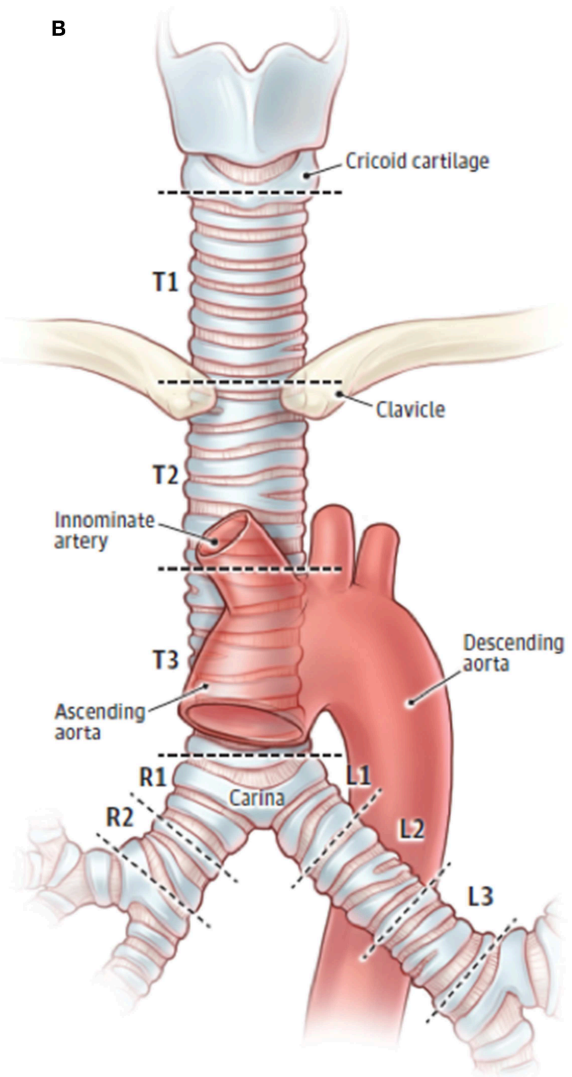

FIGURE 2 | (A) Standardized form for documentation of 3-phase bronchoscopic findings. **(B)** Anatomic divisions of the trachea and mainstem bronchi to facilitate classification and description of tracheobronchomalacia. FOE, fiberoptic examination; AE, aryepiglottic; L cleft, laryngeal cleft; T1, trachea level 1; T2, trachea level 2; T3, trachea level 3; L1, left mainstem bronchus level 1; L2, left mainstem bronchus level 2; L3, left mainstem bronchus level 3; R1, right mainstem bronchus level 1; R2, right mainstem bronchus level 2; BI, bronchus intermedius; TEF, tracheoesophageal fistula; R, right-sided; L, left-sided; LMB, left mainstem bronchus; NL, normal; ELLIP, elliptical cricoid; U, U-shaped rings; BOW, bow-shaped rings [Illustration was adapted from Choi et al. (14) Copyright 2019 by American Medical Association].

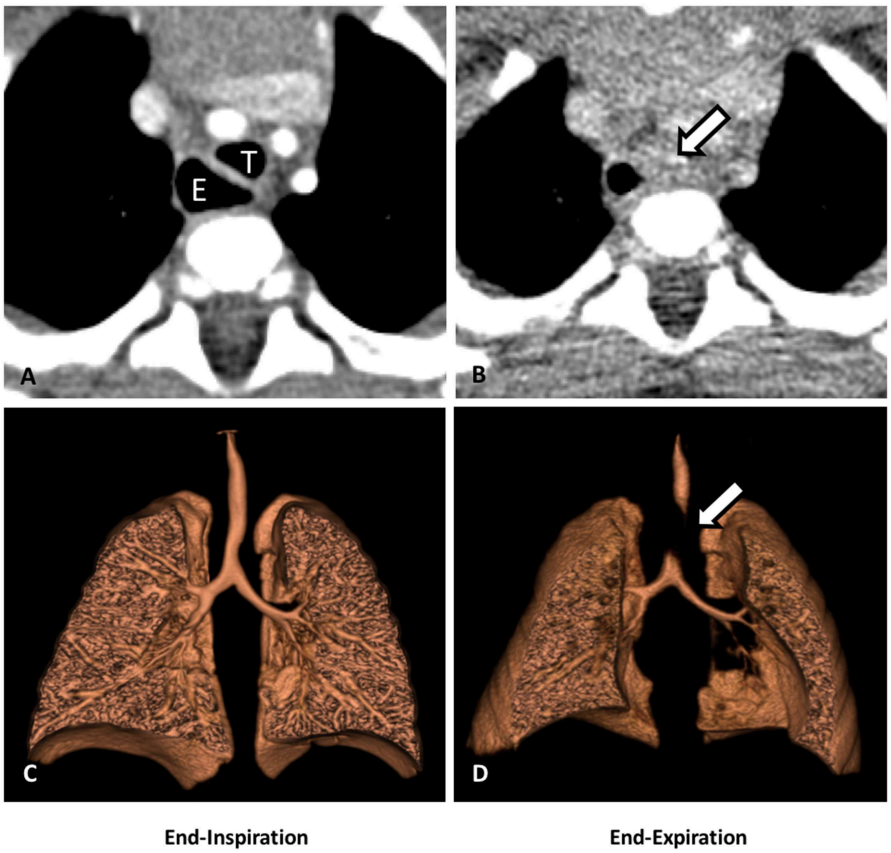

FIGURE 3 | Dynamic airway CT scan with 3-D reconstruction. **(A)** CT scan (cross-sectional view): partial collapse of the mid trachea (T) and dilated esophageal dilation (E) at end-inspiration. **(B)** CT (cross-sectional view): complete collapse of the mid trachea (arrow) at end-expiration. **(C)** 3-D reconstruction of the airways: partial collapse of the mid trachea at end-inspiration. **(D)** 3-D reconstruction of the airways: complete collapse of the mid trachea at end-expiration (arrow).

regions with forced exhalation or coughing, and those with recurrent pulmonary infections typically have complete collapse of one or more regions, causing impaired mucus clearance from the airway distal to that region.

Our team routinely uses a standardized reporting system for bronchoscopic evaluation based on anatomic regions and the severity of airway collapse. The airway has different surrounding structures throughout its course in the mediastinum. Taking these differences into account is important for a complete assessment of the airway as well as better communication with other providers. Anatomic regions are classified into the upper (T1), middle (T2), and lower (T3) trachea; and right and left mainstem bronchi. T1 is the upper third of the trachea, located above the clavicles and up to the cricoid cartilage (extrathoracic trachea). T2 is the middle third of the trachea, located below the clavicles to the takeoff of the innominate artery, which can usually be easily visualized during bronchoscopy. T3 is the lower third of the trachea, including the carina and the takeoff of the two mainstem bronchi. The right mainstem is divided into the proximal and distal right mainstem (R1, R2), and the left mainstem is divided into the proximal, middle, and distal left mainstem (L1, L2, L3). For each of these regions, we determine the percentage of airway narrowing and contribution of anterior collapse and/or posterior intrusion (13, 14) (**Figure 2**) as well as note any other airway distortion (such as lateral intrusion) or other airway lesions such as masses, cobblestoning, fistulas, etc.

In recent years, dynamic airway evaluation and angiography using a contrast-enhanced multidetector computed tomography (MDCT) with two-dimensional (2D) and three-dimensional (3D) reconstructions have become an important modality to aid in the evaluation of thoracic anomalies in pediatric patients (13, 14) (**Figure 3**). The dynamic airway evaluation can be performed in two phases of end-inhalation and end-exhalation (paired end-inspiratory and end-expiratory). Younger patients (usually under 6 years of age) may require sedation with laryngeal mask or intubation, but older patients can hold their breath (20, 32). Deep inhalation or breathe holding with 20 cm of water airway pressure is performed during the inspiration phase, and the exhalation phase is done with maximal exhalation or with zero airway pressure. The changes in the caliber of large airways are compared at both end-inspiration and end-expiration to identify the location of the TM/TBM caused by external compression (20, 33), but may not identify the severity of dynamic airway collapse due to the zero airway pressure used

(as opposed to high end-expiratory pressures during coughing). Posterior membrane intrusion may create a "frown-sign" during forced exhalation (34). CT angiogram with 3-D reconstructions helps to evaluate vascular anomalies, if present, and the airway anatomic relationships to surrounding vasculatures. We also use a modified dynamic CT angiogram to identify the artery of Adamkiewicz to avoid injury to the spinal cord during surgery. MDCT study provides important information about the location and extent of TM/TBM, as well as the surrounding intra-thoracic structures and anomalies. This information helps surgeons to better understand the region of TM/TBM and the relevant surrounding structures, such as the location of the aorta and the innominate artery relative to the trachea, and the presence of any vascular anomaly that might alter the surgical plan. However, it is important to understand that a dynamic MDCT tends to markedly underestimate the degree of airway collapse (13, 27), and therefore, it cannot be used to "rule out" TM/TBM and needs to be employed in combination with diagnostic 3-phase bronchoscopy.

Other studies that are helpful in the preoperative assessment include an esophagram to assess swallowing, strictures, and aspiration, a ventilation-perfusion (V/Q) scan to assess lung performance, and an echocardiogram to confirm acceptable heart function prior to undergoing a large surgery (31). A newer study is the nuclear clearance study, which can assess the function of the esophagus, emptying of the stomach, aspiration, and tracheal clearance.

MEDICAL MANAGEMENT

Many physicians have the opinion that symptoms may improve within a few years without surgical intervention. All patients affected by mild to severe TM/TBM may benefit from medical management. The mainstay of medical management while awaiting airway structural stability is the optimization of the ciliary clearance of secretions since the cough clearance mechanism is thwarted by airway collapse (24, 28–31). In order to optimize airway clearance, ipratropium bromide (Atrovent) is administered to minimize the secretions without thickening the secretions as may occur with glycopyrronium bromide (Robinul). Normal saline or hypertonic saline is also nebulized to thin the secretions as much as possible. We have many patients with clinical signs of cough and recurrent respiratory infections who are effectively managed on a clearance regimen and can avoid surgery. Pulmonary hygiene (formerly referred to as pulmonary toilet) and chest physiotherapy to help with mucociliary clearance, as well as control of gastroesophageal reflux (GER) to minimize aspiration of inflammatory gastric contents, are also encouraged. In patients with a history of EA/TEF, the concern for esophageal dysmotility with stagnation and bacterial or fungal overgrowth and/or GER and the need for fundoplication must be seriously considered. Concerns for recurrent or congenital tracheoesophageal fistula leading to airway contamination should be investigated. In our opinion, routine and aggressive or continuous use of corticosteroids should be avoided due to the risks of cartilage degradation and progressive tracheomalacia. Continued exposure to steroids may cause tissue weakening and progressive small airway collapse. In addition, enthusiastic use of steroids can lead to Cushingoid appearance and adrenal suppression.

There is little evidence for the benefit of bronchodilators and muscarinic agents in patients with TM/TBM. While bronchodilators are widely used for wheezy patients with reactive airway disease, administrating a beta-agonist may worsen TM/TBM by reducing the tone of airway smooth muscle, resulting in a more pliable posterior membrane (35). On the contrary, muscarinic agonists such as bethanechol and methacholine can directly stimulate the airway smooth muscle and increase the posterior membranous tone (35). However, there is no evidence supporting the clinical efficacy of pharmacologic stimulation of airway muscle tone in patients with dynamic airway collapse caused by the posterior intrusion of the membranous component.

In the past, the initial approach in patients with severe TM/TBM was the placement of a tracheostomy and long-term mechanical ventilation. Tracheostomy is not a risk-free procedure, particularly in small infants, requiring changes in the size and length of the tracheostomy tube as the child grows. Even after successful tracheostomy placement, this approach may be associated with risk of tracheal injury, inflammation-causing granulation tissue, tracheo-arterial fistula formation, tracheal stenosis, tracheal pouch formation, tracheo-esophageal fistula formation, tracheal plugging, accidental decannulation, delayed vocalization, and difficulty with decannulation as the placement of the tracheal tube does not address the problem of the collapsible airway distal to the end of the tracheostomy tube. In addition, secondary TM and tracheal fibrosis from the presence of the tracheostomy may occur. In patients with TM/TBM that extends beyond the tip of the tracheostomy tube, the utility of the tracheostomy is to be questioned since the patient will still require positive airway pressures and may continue to have blue spells and recurrent infections that can cause progression of the TM/TBM.

SURGICAL TREATMENT

A common misconception is that children outgrow TM/TBM. The truth is that TM/TBM is typically a congenital malformation of the tracheal cartilages and can sometimes slowly get less clinically serious over time, but TBM does not resolve on its own and can even get worse with age. Surgical treatment is reserved for the most severe cases and must be specific to the type and location of the TM/TBM in each patient based on the detailed diagnostic assessment protocol. All the associated conditions, such as cartilage deformation, vascular anomalies, mediastinal masses, tracheoesophageal fistula, abnormal airway branching as well as chest wall and spine deformity, should also be taken into account. Each operation needs to be customized to the airway anatomy, including decisions about the desired anatomic relationships of the trachea to the esophagus and major vasculature. Surgical options for the treatment of TM/TBM include pexy procedures (anterior

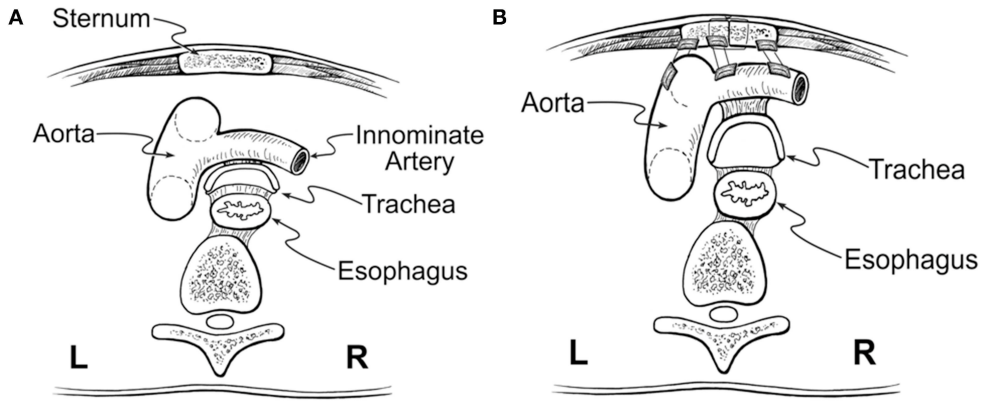

FIGURE 4 | Anterior aortopexy. **(A)** Anterior collapse of the trachea, caused by compression of the aorta. **(B)** Anterior aortopexy with suspension of both the ascending aorta and the innominate artery to the posterior surface of the sternum using pledgeted horizontal mattress sutures. This image was illustrated by Dr. John Foker and published with his permission.

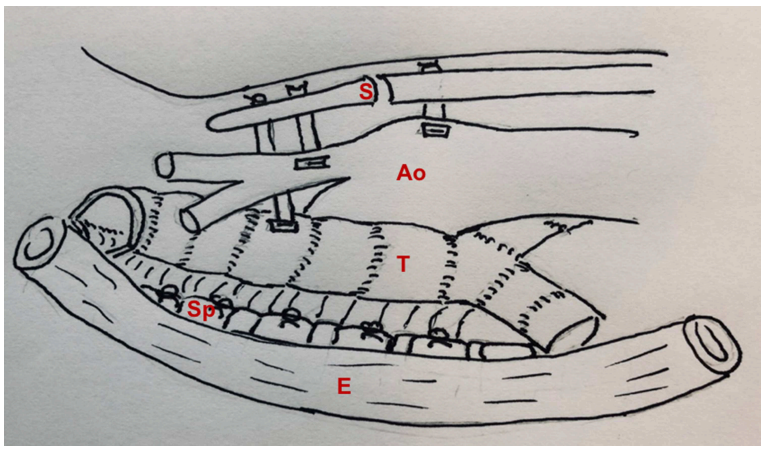

FIGURE 5 | Posterior and anterior tracheopexy combined with anterior aortopexy. S, sternum; Ao, aorta; T, trachea; Sp, spine; E, esophagus.

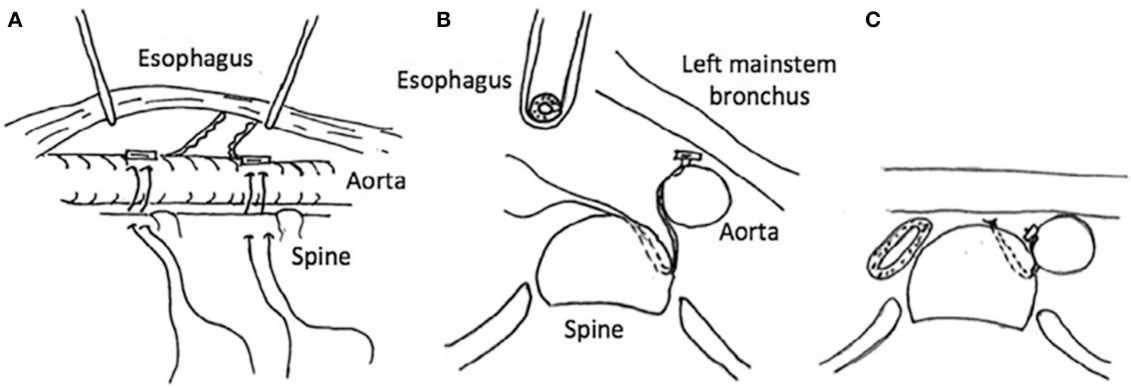

FIGURE 6 | Posterior descending aortopexy. **(A)** Anatomic relationships of the descending aorta to the esophagus and the spine. **(B)** Cross-sectional view: the esophagus is rotated to the right and the descending aorta is moved to the left and secured to the side of the spine as posteriorly as necessary to relieve posterior pressure off the left mainstem bronchus. **(C)** Descending aortopexy sutures are tied, relieving left mainstem posterior intrusion and compression between the descending aorta and the pulmonary artery.

aortopexy, anterior and/or posterior tracheopexy, anterior and/or posterior mainstem bronchopexy, posterior descending aortopexy), tracheal resection and end-to-end anastomosis or slide tracheoplasty, and placement of external splints and internal stents either absorbable or permanent (36).

Tracheomalacia has historically been addressed with anterior aortopexy. This technique was derived from the operation described by Gross in 1948 to treat the innominate artery compression syndrome and was popularized by Filler et al. (37). Through the anterior approach, after removing the thymus, the ascending aorta or aortic arch and innominate artery pulled anteriorly and then sutured to the posterior surface of the sternum (30, 38) (**Figure 4**). The airway is loosely attached anteriorly to the major vessels by areolar tissue. Aortopexy relieves the anterior compression and supports the anterior wall of the trachea through tension on the areolar tissue. This technique can also be used to suspend the pulmonary artery, innominate artery, or pericardium if the anterior airway collapse persists (31). However, aortopexy does not directly address the airway pathologies associated with TM/TBM. Anterior aortopexy may not be a sufficient strategy in the patients with dynamic airway collapse caused by the posterior intrusion of the membranous component, which is the major contributor to airway collapse in many pediatric cases. In a recent meta-analysis, aortopexy was effective in clinically improving more than 80% of children; however, 8% showed no improvement, 4% showed worsening of their symptoms, and 6% died (30).

To address this problem, our group developed anterior and posterior tracheobronchopexy to directly address anterior airway collapse and posterior membranous intrusion, respectively (28, 31, 39). Anterior tracheobronchopexy supports the anterior wall of the trachea and/or main bronchi to the sternum and anterior chest wall, whereas the posterior tracheobronchopexy fixes the posterior membrane to the anterior longitudinal spinal ligament (**Figure 5**). Tracheobronchopexy is done under direct bronchoscopic guidance to confirm the precision of suture placement by providing tracheal luminal visualization during suture placement and to avoid full-thickness sutures. To achieve optimal airway patency, patients may require airway procedures from both posterior and anterior approaches. The posterior work is preferred to be done first, allowing adequate scarring of the posterior tracheal membrane before pulling the anterior trachea in the opposite direction with anterior aortopexy and anterior tracheopexy. Our group has recently reviewed our first 98 patients who underwent posterior tracheobronchopexy through an open approach, proving bronchoscopic and clinical evidence of improvement in airway collapse (29). More recently, we have performed posterior tracheobronchopexy through thoracoscopic and robotic approaches for the treatment of TM/TBM in select individuals (40).

The effectiveness of posterior tracheobronchopexy can be limited if compression of the mainstem bronchus from the descending aorta is noted. The posterior descending aortopexy can be used to relieve left mainstem posterior intrusion and compression between the descending aorta and the pulmonary artery (41) (**Figure 6**). The posterior descending aortopexy can be performed from either the right or the left side. Most commonly, it is performed from the right side in patients with a left aortic arch as other airway work can be performed through the same incision. After mobilizing of the descending aorta, the posterior descending aortopexy is performed by passing autologous pericardial (or other tissue such as pleural or scar tissue) pledgeted polypropylene sutures to secure the aorta to the side of the spine, and as posteriorly as necessary to relieve posterior pressure off the left mainstem bronchus (41). This posterior movement of the aorta may necessitate dividing one or more intercostal arteries, and preoperative MDCT helps to avoid risking injury to the artery of Adamkiewicz.

The pediatric trachea tolerates less anastomotic tension but is more mobile than the adult trachea. Tracheal resection with either end-to-end anastomosis or as a slide tracheoplasty may be indicated in patients with some types of short-segment TBM, such as the congenital absence of cartilage or severe cartilage deformation. However, this approach is not widely used because TBM rarely affects a short segment of the trachea or bronchus.

Internal airway stents have been attempted to treat severe tracheobronchial stenosis or tracheobronchomalacia; however, the use of this technique in children has been limited due to serious complications including migration or fracture, erosion into nearby structures, formation of granulation tissue, difficult removal, and the need for additional dilations or stents, especially with patient growth (42–45). Therefore, this approach has fallen out of the favor but is still considered in highly selected patients with life-threatening airway obstruction who have failed other therapeutical strategies or in whom the risk-benefit analysis points to internal stent placement.

External splinting may offer airway support as an alternative to internal stenting in selected patients with life-threatening TM/TBM. External splints with autologous materials and prosthetic materials have been used to stabilize the malacic or deformed airway. Implantation of external prosthetic splint has raised concerns in terms of long-term effects and complications, including infection and erosion into nearby structures (46). An external splint made from the molded resorbable plate can be sutured around the airway, providing temporary airway support with full resorption predicted to occur within 1–3 years (47). This hopefully allows enough time for the cartilages to reform in a more favorable shape and allows for the growth of the airway in the pediatric patient. Interesting work in this field has been performed by Dr. Green's group in Michigan. They introduced both resorbable and permanent custom-printed external splints for the treatment of severe tracheobronchomalacia (47–50). Using a CT scan and custom software with 3-D reconstruction of the airways, a polycaprolactone or nylon splint is created and then secured around the trachea or bronchus to keep the airway open. A recent study published by this group reported the clinical efficacy of the 3D-printed bioresorbable airway splint device in a series of critically ill children with severe tracheobronchomalacia (50). The Esophageal and Airway Treatment (EAT) Center has been using the moldable bioresorbable plates (RapidSorb, Synthes CMF) to make intra-operative customized external splints in patients found to have airway compression or deformation not alleviated by anterior or posterior airway pexy placement. Many of these patients had complex airways

which also required slide tracheoplasty or bronchoplasty, and/or anterior and posterior tracheobronchopexy.

CONCLUSIONS

Tracheobronchomalacia is a clinically challenging condition, frequently undiagnosed or misdiagnosed in pediatrics, and includes many airway pathologies that cause either fixed or dynamic airway narrowing. Patients are best assessed and managed by a multidisciplinary team in centers specializing in complex pediatric airway disorders. The treatment plan should be individualized with a thorough approach to the underlying pathology and clinical concerns. All patients warrant aggressive medical management. For those children considered candidates for surgical intervention, three-phase dynamic bronchoscopy, and dynamic airway CT showing the position of vessels and other important landmarks in the mediastinum are helpful in surgical planning.

AUTHOR CONTRIBUTIONS

AK and RJ: study conception and design and critical revision. AK: drafting of the manuscript.

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REVIEW
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Endoscopic Preoperative Assessment, Classification of Stenosis, Decision-Making

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Pediatric Laryngo-Tracheal Stenosis (LTS) comprises different conditions that require precise preoperative assessment and classification. According to the guidelines, the optimal diagnostic work-up of LTS patients relies both on a comprehensive anamnesis and on endoscopic and radiological assessments. All the causes of LTS result in an impairment in airflow, mucociliary clearance, phonation, and sometimes in swallowing disorders. The main goals of treatment are to maintain an adequate respiratory space and restore the Upper Aero-Digestive Tract (UADT) physiology. The first step when dealing with LTS patients is to properly assess their medical history. The main causes of pediatric LTS can be divided into two groups, i.e., congenital and acquired. The most common causes of congenital LTS are: laryngomalacia (60%), vocal fold paralysis (15–20%), subglottic stenosis (SGS) (10–15%), laryngeal webs and atresia (5%), subglottic hemangioma (1.5–3%), and others. On the other hand, 90% of acquired pediatric LTS cases are subsequent to post-intubation injuries. Other less frequent causes are: iatrogenic complications from endoscopic laryngeal interventions, benign tumors, caustic or thermal injuries, external blunt force injury or trauma, chronic inflammatory disorders, or idiopathic causes. Diagnostic work-up consists in a step-by-step investigation: awake and asleep transnasal fiberoptic laryngoscopy (TNFL), direct laryngoscopy with 0° and angled telescopes to investigate the type of stenosis (arytenoid mobility, craniocaudal extension, involved anatomical sites, and active or mature scar tissue), and broncho-esophagoscopy to rule out associated mediastinal malformations. To date there are several available classifications for each of the involved sites: Cohen's classification for anterior glottic stenosis, Bogdasarian's for posterior glottic stenosis (PGS) and Myer-Cotton's for subglottic stenosis, even though others are used in daily practice (Lano-Netterville, FLECS, etc.). The European Laryngological Society recently proposed a new classification which is applicable in all LTS cases. In this chapter we deal with preoperative assessment and staging, reviewing the most relevant classifications applicable in patients affected by LTS, *conditio sine qua non* in order to tailor the best treatment modality to each subject. We'll also detail the comprehensive radiological, endoscopic and functional assessment for the correct use of each staging classification.

Keywords: classification, laryngotracheal stenosis, decision-making, pediatric airway, European laryngological society

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INTRODUCTION

Pediatric laryngotracheal stenosis (LTS) comprises a wide number of conditions that require precise pre- and intraoperative assessment.

The main causes of pediatric LTS can be divided into two groups, i.e., congenital and acquired. The most common causes of congenital LTS include laryngomalacia (60%), vocal fold paralysis (15–20%), subglottic stenosis (SGS) (10–15%), laryngeal webs and atresia (5%), subglottic hemangioma (1.5–3%), and others (1). On the other hand, 90% of acquired pediatric LTSs occur after post-intubation injuries. Other less frequent causes include iatrogenic complications from endoscopic laryngeal interventions, benign tumors, caustic or thermal injuries, external blunt force injury or trauma, chronic inflammatory disorders or idiopathic causes (2).

The aims of the initial assessment are to establish or confirm the diagnosis, to identify disease-specific risk factors and prognostic variables, to set goals with the patient and his/her parents and to establish an initial management plan (3).

Accurate preoperative and intraoperative diagnostic work-up is of paramount importance to obtain crucial information which could impact on the postoperative outcome. Information that must be collected includes vocal fold mobility, the presence of glottic and/or supraglottic scar tissue, crico-arytenoid joint(s) fixation, possible additional tracheal damage (stenosis, malacia) related to stoma or cannula, secondary airway lesions (i.e., granuloma, scar tissue), obstructive sleep apnea (OSA)-related obstructions, swallowing difficulties with/without chronic aspiration, severe gastroesophageal reflux (GOR), eosinophilic esophagitis, medical comorbidities, or congenital anomalies.

Any of the following scenarios may be encountered in a child with acquired LTS: (1) neonatal intubation for respiratory distress; (2) intubation for infection or traumatic injury later in life; (3) previous history of endotracheal intubation presenting as "idiopathic" LTS (4).

An important distinction that must be pointed out is between incipient and mature stenosis. Incipient LTS results from acute or subacute post-intubation airway narrowing (e.g., edema, ulcerations, granulation tissue), which is treated endoscopically or by a cricoid split procedure in newborns in an effort to prevent cicatricial stenosis. The final goal is to avoid tracheotomy or allow decannulation in already tracheostomized patients (2).

Mature cicatricial stenoses correspond to well-established airway narrowing that can pose a therapeutic challenge to the surgeon. It is thus of paramount importance to understand the individual characteristics of the stenosis and the clinical context of each patient (5).

In order to identify the best therapeutic option, an appropriate diagnostic work-up must include correct staging of the lesion and an endoscopic pre- and intraoperative assessment.

CLASSIFICATIONS OF LTS

In the last few decades, the broad variety of laryngotracheal stenosis presentations has been in great need of standardized definitions. In an attempt to fill this gap, laryngotracheal stenosis classifications have proliferated in the literature due to the need to describe the complex anatomy of this district, the varied clinical presentations and the treatment possibilities. The most relevant classifications are reported in this chapter.

Myer-Cotton

This classification was proposed by Myer et al. (3), taking cues from a previous version published by Cotton (4). The Myer-Cotton classification was intended for firm, mature subglottis stenoses, thus excluding any other lumen narrowing conditions (e.g., trachea- and/or laryngomalacia, vocal cord paralysis, immature stenosis, tracheal stenosis, suprastomal collapse, supraglottic collapse and suprastomal granulation tissue). While it was initially used to predict lumen surface reduction in case of endotracheal tube application, it was then extended to describe both pediatric and adult subglottic and/or tracheal stenosis. It consists of IV grades: Grade I—0 to 50% decrease in lumen surface; Grade II—51 to 70% decrease; Grade III—71 to 99% decrease, and Grade IV–no evidence of detectable lumen (**Figure 1**). Healthy and stenotic lumen surfaces can be accurately calculated and compared by radiological imaging or intra-operative investigation using the formula $A = \pi r^2$ to obtain circle area values.

McCaffrey

In 1992, McCaffrey proposed a classification to describe the extension of the stenosis among the most commonly involved subsites: glottis, subglottis and trachea (6). This system was initially validated on an adult population but was later extended to pediatric patients. This classification was conceived after both univariate and multivariate analyses showed that the involved site had the most consistent significant predictive value for determining time to decannulation. Stage I is located in the subglottis or trachea, with a craniocaudal extension of <1 cm. Stage II stenosis is limited to the subglottis and has a craniocaudal extension of more than 1 cm. Stage III stenosis involves both the subglottis and trachea, while Stage IV stenosis extends to the glottis with fixation or paralysis of at least one vocal cord (**Figure 2**).

Lano-Netterville

In 1998, Lano et al. (7) proposed a simpler staging system based on anatomical subsite involvement. The authors described three stages according to the number of involved subsites: Stage I in case of single subsite involvement, stage II for two involved subsites and stage III in case of glottic-tracheal involvement (**Table 1**). The Authors recommended the use of this classification in order to have a good correlation between surgical success and stage categories, which in their retrospective population resulted 94, 78, and 20% for Stage I, II, and III, respectively.

Cohen

A new classification proposed by Cohen (8) attempted to describe anterior glottic webs occurring at the time of glottic lumen formation during laryngeal embryological development (1985). The four types of anterior glottic web correlate with the severity of symptoms. Type 1 is an anterior web involving 35% or less of the glottic lumen. Type 2 ranges between 35 and 50%, Type 3

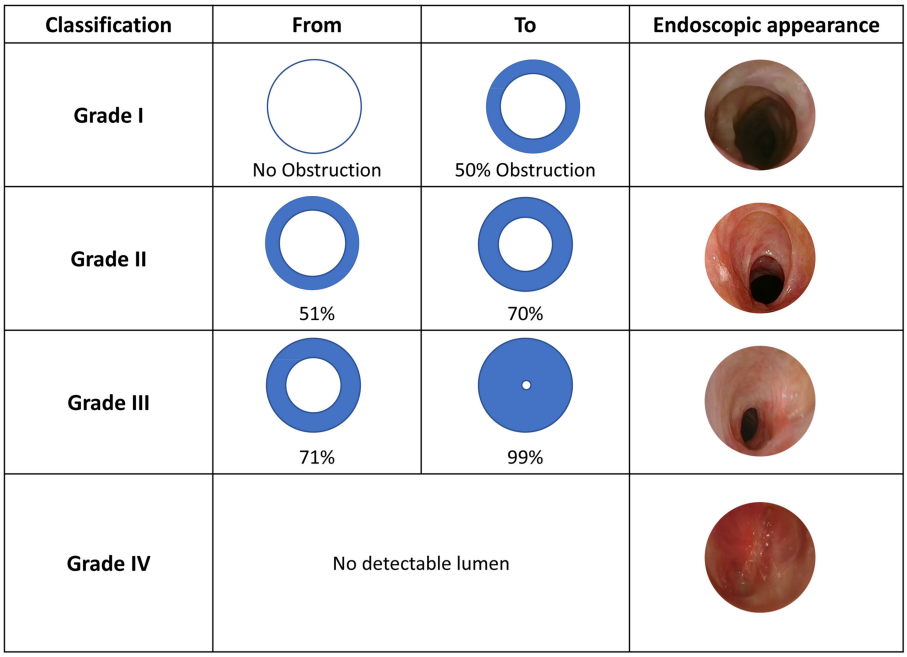


FIGURE 1 | Myer-Cotton classification, adapted from Myer et al. (3) with unpublished clinical pictures.

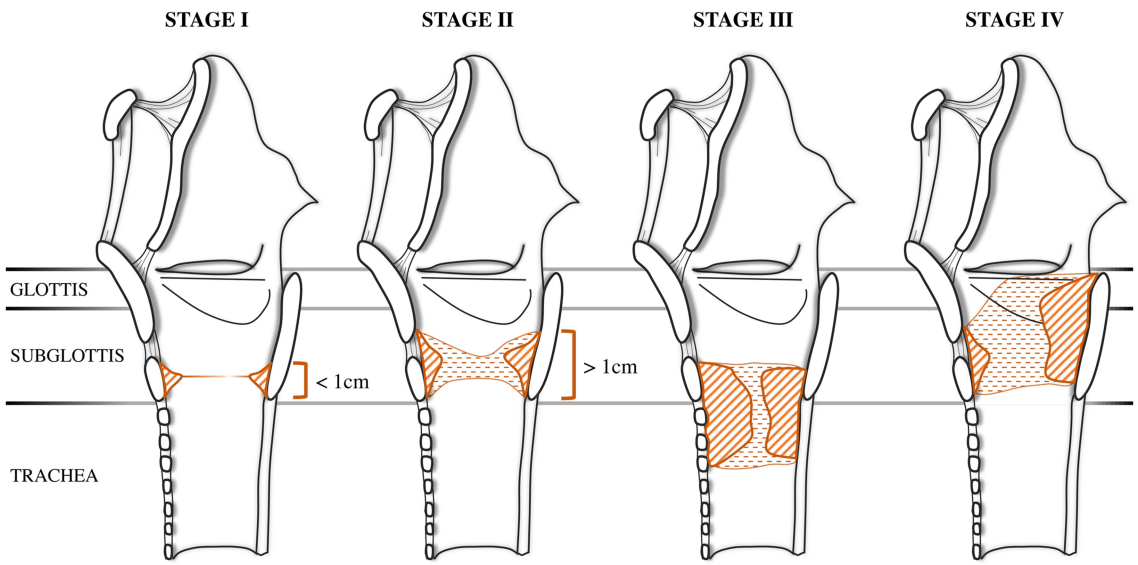


FIGURE 2 | McCaffrey Classification. The stenosis can be located in the subglottis or in the trachea in stage I and in stage II, adapted from McCaffrey (6) with unpublished draws.

between 51 and 75% while Type 4 involves 76% or more of the glottic lumen (**Figure 3**).

Other Classifications

As previously mentioned, other classifications have been proposed, and while each of them describes stenotic lesions differently, they have limited relevance in clinical practice.

Laccourrey et al. (9) proposed a detailed staging system taking into account larynx fixation, subsites, and laryngeal joint involvement.

Bogdasarian et al. (10) published a new classification to describe post-intubation posterior glottic stenosis (PGS) in the pediatric population. Moreover, the FLECS staging system (11) was proposed by the American Society of Pediatric Otolaryngology (ASPO) to encompass a detailed description of

the Function, Lumen, Diameter, Extent and Site of stenosis. Although this classification was probably the most complete, it was abandoned because it was considered too confusing.

With regard to laryngomalacia, the most widely used classification was proposed by Olney et al. (12). Type 1 corresponds to a prolapse of the mucosa overlying the arytenoid cartilage, type 2 to foreshortened aryepiglottic folds and type 3 to posterior displacement of the epiglottis.

ELS Classification

In 2015, the European Laryngological Society (ELS) published a consensus paper (5) presenting a five-step endoscopic airway assessment and a reporting system. The authors attempted to standardize the pre- and intraoperative assessment techniques in order to fully investigate the lesion in all its aspects (type of stenosis, involved subsites, extension, laryngeal motility, and airway lumen). Furthermore, other conditions describing airway pathological status or concurrent comorbidities were integrated to help provide a more comprehensive evaluation of the patient.

TABLE 1 | Lano-Netterville classification Lano et al. (7).

	N. of involved subsites	Subsites
Stage I	1	Glottis or sub-glottis or trachea
Stage II	2	Glottis and sub-glottis or sub-glottis and trachea
Stage III	3	Glottis and sub-glottis and trachea

All these data are enclosed in a practical checklist which generates a final score.

The ELS classifications has been applied to large retrospective cohorts from the centers that contributed to its developing and it was confirmed to be as accurate for the prediction of both peri-operative outcome, i.e., complication rate or need for further treatments as long as for long-term outcomes, i.e., decannulation rate, both in pediatric (13) and adult groups (14) affected by laryngotracheal stenosis, and treated by tracheal or crico-tracheal resection and anastomosis. Its value for the prediction of the outcomes of patients submitted to endoscopic treatments has not been assessed yet.

The endoscopic work-up for LTS according to the ELS consists of five key-point procedures:

1. Awake indirect laryngoscopy or transnasal fiberoptic laryngoscopy (TNFL);
2. Asleep TNFL;
3. Direct transoral laryngotracheoscopy with a bare zero-degree rod-lens telescope;
4. Suspension microlaryngoscopy;
5. Bronchoesophagoscopy;

See the next paragraph for a detailed description of each step (5).

Radiological Assessment

Unlike indications for radiological evaluation in adult patients, those for pediatric stenosis are still under debate. CT scan can be helpful for studying craniocaudal extension and severity of the obstruction, capable to provide also 3D reconstruction of the airways (15, 16), especially when awake TNFL is unable

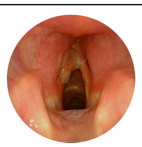
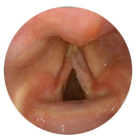
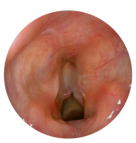
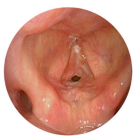
Classification	From	To	Endoscopic appearance
Grade I	No Obstruction	35% Obstruction	
Grade II	35%	50%	
Grade III	51%	75%	
Grade IV	76%	100%	

FIGURE 3 | Cohen Classification, adapted from Monnier et al. (5) with unpublished clinical pictures.

to show a clear view of them. Indeed, before performing any procedure under sedation or general anesthesia, radiological investigation is always mandatory in patients with Cotton-Meyer grade III or IV stenosis, except for subjects requiring immediate tracheotomy. Good quality imaging can be obtained without sedation using a CT scan with ultrafast acquisition frames. Otherwise, radiological imaging is indicated to study neck masses or abnormal mediastinal vessels (17). If the child can be safely sedated, standard CT or MRI scans can be performed in the presence of an anesthetist. MRI provides high resolution images allowing the assessment of airway compression secondary to mediastinal malformations (5).

Functional Assessment

Voice evaluation and respiratory function assessment should be obtained before carrying out any conservative or open neck procedures in order to establish the baseline condition. Documentation regarding stridor at-rest or during exercise, and physical activity and pulmonary function tests, such as spirometry, must be reported (18). Moreover, voice evaluation should be performed using the GRBAS-scale, including voice range profile and maximum phonation time for the vowels/e/and/a/. In case of infant patients these clinical data are meaningless if the tests cannot be performed properly (5).

Assessment of the Patient's General Condition

A comprehensive assessment of concomitant comorbidities must be included in the work-up. Pulmonary and cardiac check-ups are required, together with a full neurological evaluation. In case of previous tracheostomy, the grade of stenosis can easily be tested by temporarily occluding the cannula. This test provides immediate feedback on pulmonary capacity and low-flow/high-pressure resistance of the stenotic area (5).

Final Scoring

ELS final scoring is obtained by combining the Myer-Cotton grading system, a revised version of the Lano-Netterville classification, and the presence of severe comorbidities. The Myer-Cotton score defines the degree of stenosis and, similarly to the original classification, assigns a value from I to IV.

Thereafter, a revised version of the Lano-Netterville classification, which includes the supraglottis as the fourth subsite, is applied: (a) establishes a single subsite involvement and so forth up to (d) for involvement of all subsites. Lastly, in case of severe comorbidity or congenital abnormalities, a (+) sign is added to the score (**Figures 4**, **5**) (5).

Advantages and Limits of ELS Classification

The main advantage of ELS classification is its comprehensive value and its aid guiding the whole work-up for a patient affected by laryngotracheal stenosis; regarding the scoring system it introduces the three-dimensional view, taking into account together the cranio-caudal shape of the stenosis and its smaller area on the axial plane; furthermore, relevant comorbidities of the patient are included, as they are crucial for the correct decision-making process. Beyond all these favorable features of the ELS classification, it has some limits as it lacks specificity for some subsites of the airway, such as the different compartments of the glottis, for which the older Cohen's and Bogdasarian's classification still play a relevant role for the staging of anterior and posterior glottic stenosis, respectively. Secondary, the functional investigation, such as spirometry, is included in the suggested work-up but its specific parameters are not taken into consideration in detail; beneath this kind of test is mostly applicable in adults population, the results by the recent literature about the usefulness of such exam are rising the value of spirometry for an objective evaluation of patients both for the pre-treatment staging and for follow-up period (19, 20).

PREOPERATIVE ENDOSCOPIC ASSESSMENT

The endoscopic diagnostic work-up includes TNFL, asleep TNFL, direct transoral laryngoscopy with 0° and 70° telescope, suspension microlaryngoscopy (SML), and bronchoesophagoscopy. Upon completion of the endoscopic work-up, a radiological study with CT and/or MRI must be performed, as must an assessment of respiratory and voice function and of the patient's general conditions.

Transnasal Fiberoptic Laryngoscopy

TNFL is part of the in-office examination. Patency of the nasal cavities, choanae, nasopharynx, pharynx, and larynx should be carefully assessed.

Flexible nasoendoscopy is performed to detect any obstructive supraglottic lesions (e.g., laryngomalacia, lymphovascular malformations, and cysts), vocal fold movements, and any evidence of impaired swallowing such as hypopharyngeal pooling of secretions. If restricted abduction or true immobility is observed, then a complete examination under general anesthesia is warranted in order to distinguish neurogenic bilateral vocal cord paralysis from posterior glottic stenosis, especially if the patient has been subjective to an orotracheal intubation. TNFL always yields incomplete information as the subglottis and trachea cannot be properly visualized.

Not all patients need direct laryngoscopy, especially when a clear diagnosis of mild laryngomalacia is made following a comprehensive medical history and physical examination (21). However, in case of symptom worsening, associated abnormalities or atypical clinical presentations, a complete laryngotracheobronchoscopy and esophagoscopy must be performed under general anesthesia.

Asleep TNF

Clinical indicators such as feeding difficulties, growth slowdown, obstructive sleep apneas and pulmonary hypertension required further investigation. Moreover, inadequate patient compliance is an absolute indication for TNFL under general anesthesia but in spontaneous respiration. Anesthesia is maintained with sevoflurane or i.v propofol. Before starting the laryngoscopy, atropine is administered intravenously.

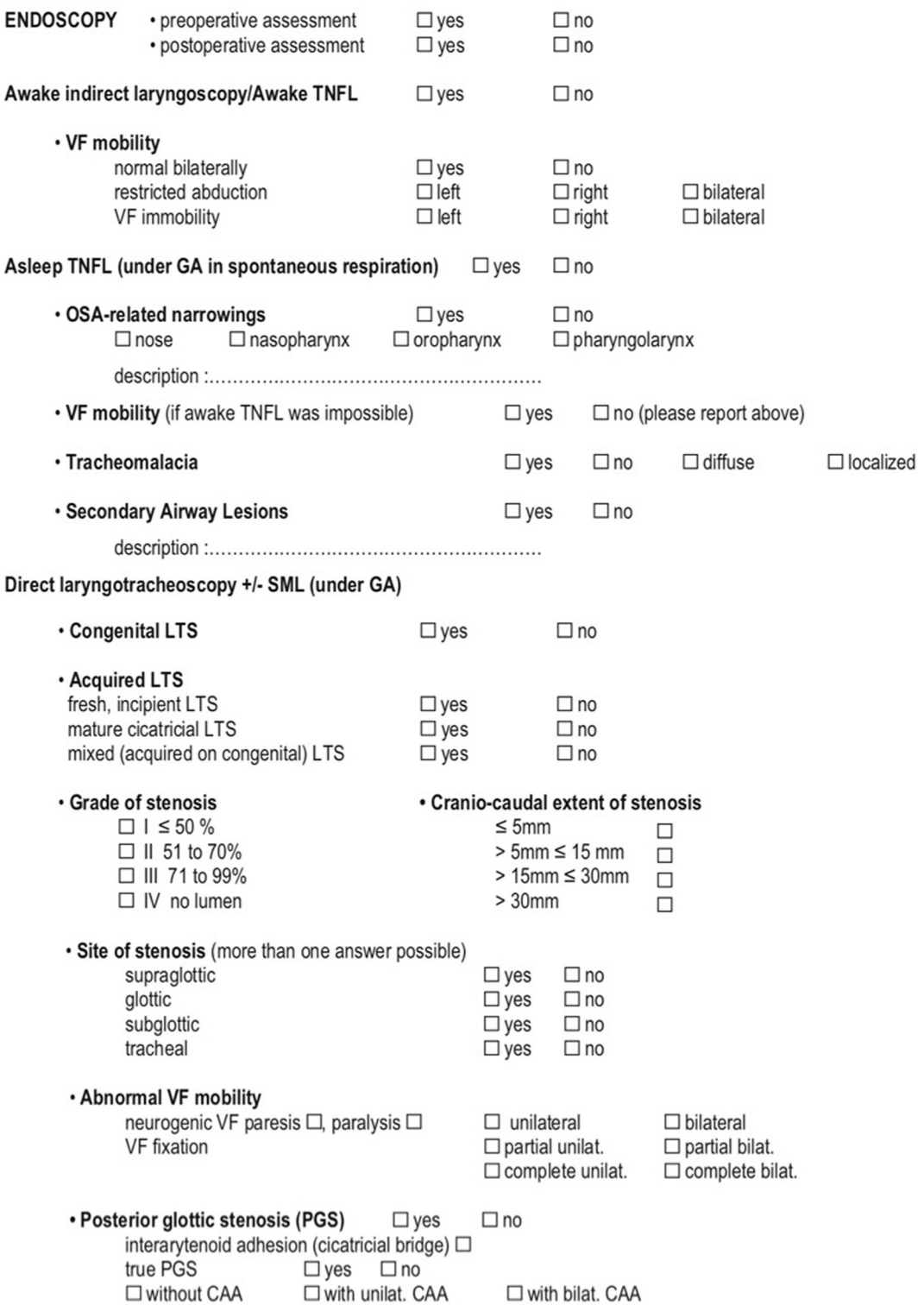


FIGURE 4 | ELS checklist for pre-operative assessment and decision making (1/2) Monnier et al. (5).

Inspection of the nasal cavities on both sides is mandatory to identify possible pathologies, such as vestibular stenosis, deviated septum, choanal atresia, adenoid hyperplasia, or tumor masses. In cases of obstructive sleep apnea, when patients undergo general anesthesia with spontaneous breathing, their muscle tone decreases and the level of obstruction can then

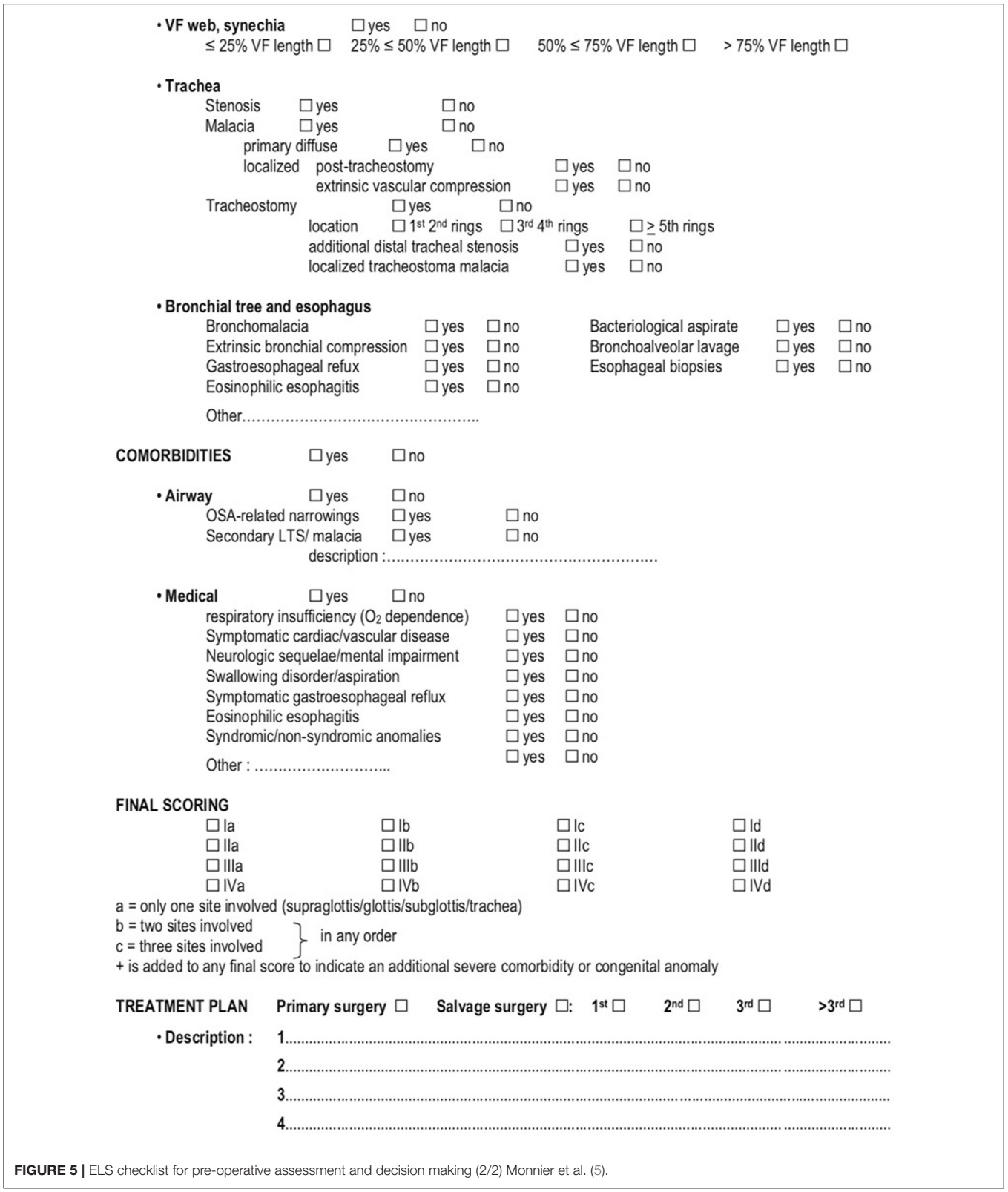


FIGURE 5 | ELS checklist for pre-operative assessment and decision making (2/2) Monnier et al. (5).

be identified. Various causes of dynamic obstruction that are detectable by fiberoptic endoscopy include retroposition of the soft palate, lingual tonsillar hypertrophy and epiglottic and supraglottic prolapse. This assessment is extremely relevant, especially in the preoperative evaluation of subglottic stenosis. A jaw lift is mandatory to raise the tongue base, allowing a

better visualization of the pharyngolarynx. When the video-bronchoscope reaches the laryngeal aditus, deeper anesthesia is needed in order to further advance into the lower airway tract without risking laryngospasm.

Passing behind the epiglottis and reaching the laryngeal inlet allows for a detailed and careful assessment of vocal cord mobility (22): it should be noted that large cuneiform cartilage and short aryepiglottic folds can obscure the laryngeal inlet and prevent a proper view of the vocal cords. Flexible laryngoscopy in the office setting might not be able to identify oropharyngolaryngeal obstructions that may be responsible for OSA.

Evaluation of the larynx during spontaneous breathing allows us to identify webs, posterior glottic stenosis, vocal fold palsy or paralysis.

Furthermore, dynamic examination of the trachea and bronchi is of paramount importance for the diagnosis of localized or diffuse tracheomalacia and anatomical narrowings of the lower airways. When vocal cord immobility is detected during TNFL, SML must be carried out.

In conclusion we can say that both awake and asleep TNFL are required in the evaluation of a compromised airway.

Direct Transoral Laryngoscopy With 0° and 70° Telescope

In order to better visualize and characterize a possible glottic, subglottic or tracheal stenosis the child must be deeply anesthetized and completely paralyzed. The larynx is visualized using a general-purpose Storz laryngoscope with the blade inserted at the level of the vallecula. A rigid 4 mm diameter magnifying telescope offers a clear view of the endolarynx, subglottis and trachea as far as the carena. In case of subglottic or tracheal stenosis, attention has to be paid not to damage the mucosa. Indeed, the slightest injury to a narrow airway could decompensate a stable obstructive dyspnea, thus requiring a tracheotomy. If the 4 mm diameter endoscope is too large, then a 2.7 mm or even a 1 mm diameter (sialendoscopy) scope should be used to assess the length of the stenosis and the integrity of the distal airway. The degree of SGS is calculated by passing telescopes or bougies of different sizes through the stenosis. The Myer–Cotton airway grading system is commonly utilized (3). Generally speaking, a tracheostomy caused by diagnostic upper airway endoscopy must be considered unacceptable.

Suspension Microlaryngoscopy

The Benjamin-Lindholm laryngoscope is preferable for visualizing the pharynx, larynx, and subglottis (23).

Specific tools are needed during the procedure: 0° and 70° telescopes, a Lindholm vocal cord retractor, angulated probes, and tapered bougies.

Telescopes are used to measure the craniocaudal extension of the stenosis. Bougies of given size are used to measure the degree of the stricture. Lastly, in order to distinguish between bilateral vocal cord paralysis (BVCP) and posterior glottic stenosis, Lindholm vocal cord retractor and angulated telescopes are used. To get the most precise measurement of the craniocaudal extension of the stenosis, the telescope is inserted through the laryngoscope and further advanced as far as the vocal cords, pointing the distance on the shaft of the telescope. Repeated measurements are taken at the upper and lower borders of the stenosis and tracheostoma, if present, and lastly at the level of the carina (**Figure 6**). In order to program the surgery correctly, especially in case of tracheal resection and anastomosis, such measurements are mandatory. With complete airway obstruction, CT scans with 3D reconstructions are very useful.

Once we had carefully assed the craniocaudal extension and the degree of the stenosis, differential diagnosis between BVCP and PGS is mandatory. Important information can be provided by the patient's medical history. Lindholm cord retractor and an angulated probe are used to precisely assess the posterior laryngeal commissure and cricoarytenoid joint function in all the patients who have previously undergone orotracheal intubation. The former is placed at the level of the vocal fold and is opened. In patients with neurogenic BVCP, the interarytenoid distance is restored to its normal size, while in patients with PGS it remains narrow, and a stretched band of scar tissue may be observed (**Figures 7A,B**).

By using the angulated probe, it thus becomes possible to precisely identify the different types of PGS according to Bogdasarian's classification (**Figure 8**) (10).

Bronchoesophagoscopy

The diagnostic work-up of children affected by SGS must be completed by the evaluation of lower airways and esophagus. In case of tracheostomized patients, rigid or flexible bronchoscope has to be introduced through the tracheostoma. If the distal end of the cannula has caused strictures of the lower trachea, the rigid bronchoscope is not advanced any further in order to avoid mucosal damages. In this case the use of a flexible bronchoscope is mandatory. If the tracheal wall has not been damaged by the cannula, then all of the rings can be identified. The linear measure between the lower border of the tracheostoma and the carina should be measured as described in the previous paragraph (**Figure 6**). When planning possible resection and anastomosis of the airway it is of paramount importance to count the number of residual normal tracheal rings. Further investigation down to the basal bronchi is performed on both sides.

Biopsies and bronchoalveolar lavage (BAL) should always be executed at the end of bronchoscopic evaluation, as bleeding might affect any further examination.

During the bronchoscopy we have to investigate the presence of congenital or acquired lesions such as tracheo-esophageal fistula, bronchus suis, localized or diffuse malacia, extrinsic compressions, anomalous distribution of the bronchial tree and lesions caused by local trauma induced by the tracheostomy cannula as well as from suction catheters at the level of the carina. The characteristics of bronchial secretions (serous, mucus, muco-purulent) and mucosa (inflammation and friability) must be documented. Precise assessment of their effects on the ventilation through the stenotic segmental bronchi is required. Bacteriological testing of the aspirate should be conducted systematically, while BAL is necessary to confirm the diagnosis of chronic aspiration when lipid-laden macrophages are seen on the smear examination. Missing the diagnose of infection of the

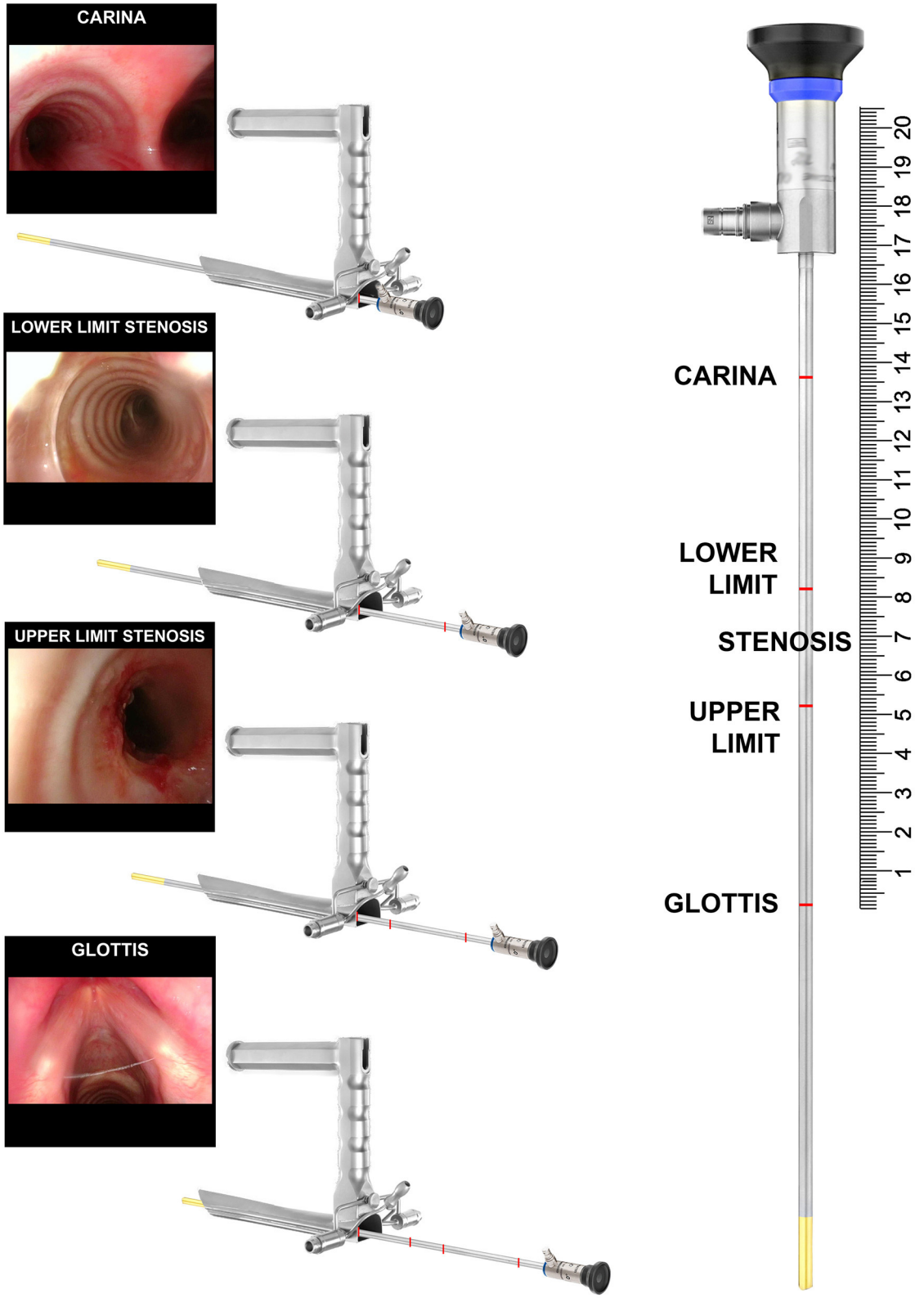


FIGURE 6 | Intraoperative measurement of a 3 cm tract of the tracheal stenosis during suspension microlaryngoscopy.

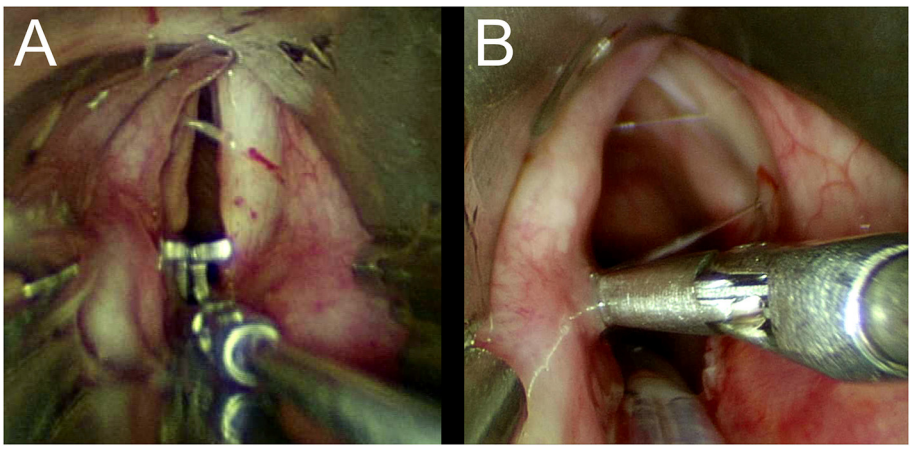


FIGURE 7 | (A,B) Lindholm cord retractor.

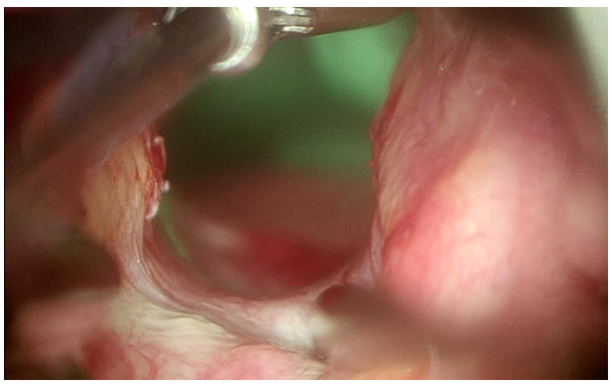


FIGURE 8 | Angulated probe to better visualize the posterior commissure.

lower airways could affect surgical outcome, leading to adverse complications such as anastomotic dehiscence, cartilage graft infection and secondary tracheostomy.

As well as bronchosocopy, esophagoscopy can be performed with flexible or rigid scopes. The use of rigid scope is easier in infants and children than in adults (24, 25).

Esophagoscopy must address the presence of gastroesophageal reflux and eosinophilic esophagitis.

GOR is best diagnosed using 24-h pH monitoring or impedancemetry, but endoscopy may reveal signs of erosive esophagitis (25). The absence of the angle of His, with the cardia opening located in a direct line to the gastric pouch, is an anatomical pattern that may cause chronic reflux.

Thickened or annulated mucosa may be indicative of eosinophilic esophagitis (26). Biopsies are necessary to confirm this diagnosis.

DECISION MAKING

Comprehensive pre-operative assessment is helpful for identifying which children affected by laryngotracheal stenosis would most benefit from surgery. It would also be useful to the multi-disciplinary laryngotracheal stenosis board team made up of ENT surgeons, pulmonologists, gastroenterologists, cardiologists, neurologists, neonatologists, and intensivists in making the best choices regarding type and timing of surgery (2). The goal of any laryngotracheal surgical procedure is to achieve decannulation and to re-establish an airway while preserving adequate laryngeal function for airway protection, swallowing, and voicing (27).

Tracheotomy

Patients affected by mild stenosis (grade I-II) are often kept under observation due to the lack of severe symptoms and pending airway growth that usually leads to widening of the free lumen. If the patient's respiratory condition starts deteriorating it is advisable to take airway reconstruction surgery into consideration to avoid a tracheotomy, the latter making further treatment more challenging and being a potential worsening factor for learning effective communication in a growing child.

In some cases, however, tracheotomy is unavoidable in order to safely secure a compromised laryngeal airway, especially in the presence of local or systemic medical conditions which are contraindicated in airway reconstruction surgery (28). It must be highlighted that the mortality rate of tracheostomized children with significant laryngeal obstruction has decreased from 24% in the 1970s to 2–3% by the year 2000 (2). When dealing with a laryngeal stenosis, the tracheotomy should be placed immediately below the cricoid to maximally preserve the normal trachea distally, or far below, sparing a sufficient amount of uninvolved tracheal rings between the stenosis and the tracheostomy. With this aim in mind, the best site to perform the procedure in patients with purely tracheal stenosis is through the stenotic site, maximally preserving the uninvolved tracheal rings.

Surgical Timing

The main factors affecting the choice to proceed to surgery primarily regard open neck laryngo-tracheal reconstruction procedures, meaning partial cricotracheal resection and

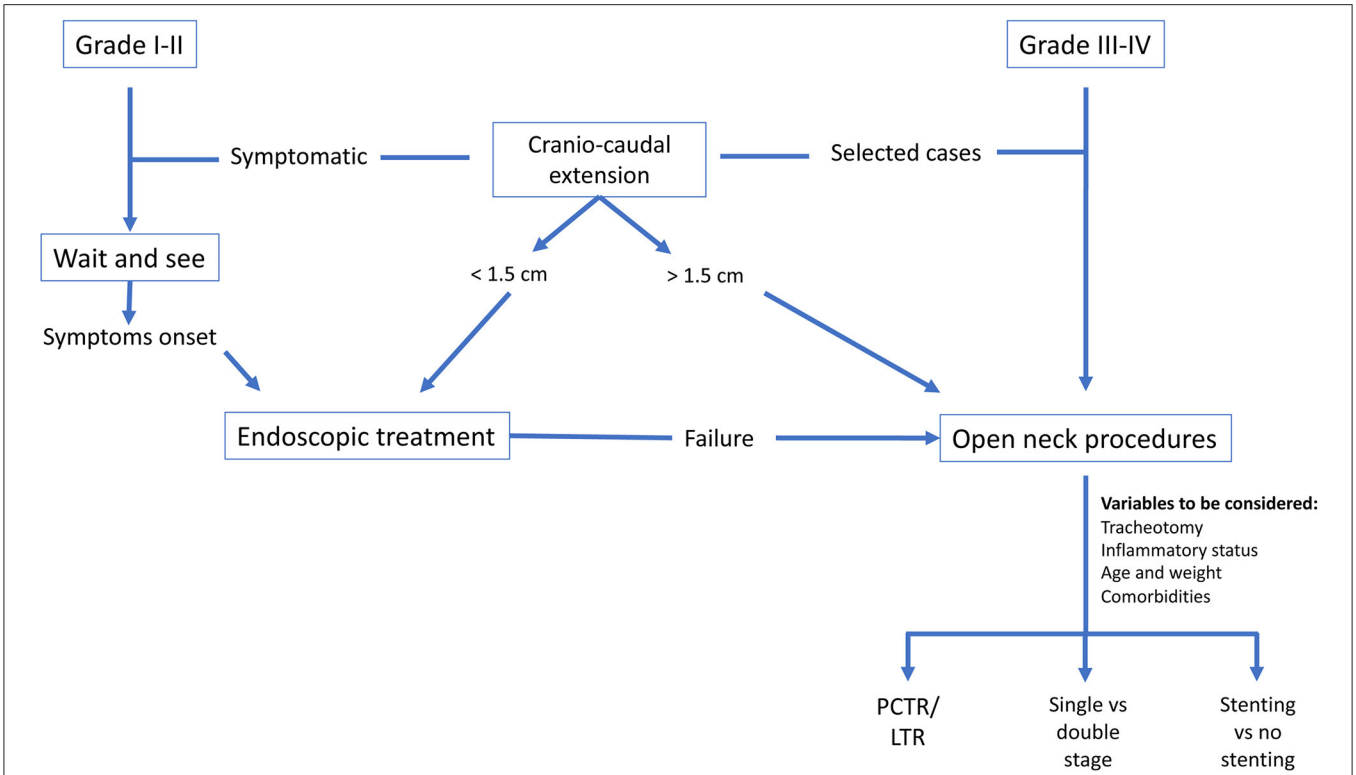


FIGURE 9 | Decision-making flow-chart.

anastomosis (PCTR) or laryngotracheal reconstruction (LTR), and can be summarized in three main items: grade of stenosis, inflammatory status of the stenosis and/or medical comorbidities, age and weight of the child.

1. Grade: for children affected by mild stenosis (Grade I-II) a wait and see policy can be chosen, especially facing with congenital, knowing that the airway is expected to become wider with growth. Endoscopic follow-up should be done every 6 months, until complete resolve of the symptoms. If a worsening of the respiratory condition is seen, an airway reconstruction surgery must be taken into account, to avoid emergency tracheostomy, potentially compromising further airway reconstructive procedures (2);
2. Inflammatory status and comorbidities: the presence of laryngeal or tracheal reactivity, as proven by the presence of erythematous mucosa or edema, is a contraindication for proceeding to open neck surgery; the same policy should be followed if the child is suffering from unresolved concomitant cardiopulmonary disease, neurological impairment associated with pharyngolaryngeal discoordination and/or aspiration or uncontrolled gastroesophageal reflux disease.
3. Age and weight of the child: when an infant has no significant comorbidities, early intervention during the first months of life is appropriate (2). Thanks to the established use of magnification devices and the experience that has been accrued in tertiary referral centers for the treatment of infants weighing <10 kg (29), the weight criterion no longer needs to be considered an absolute contraindication. As we are dealing with growing tracheostomized children, it must always be kept in mind that a delay would ultimately affect both communication learning (30) and the mortality rate associated with the tracheostomy tube.

Patient Management

Currently available treatments can be summarized as including endoscopic procedures, open neck laryngo-tracheal reconstruction (single stage/double stage PCTR/LTR) and the use of non-surgical devices, such as continuous positive airway pressure (C-PAP) therapy. Patients with mild stenosis (grade I-II) often have intermittent stridor associated with respiratory tract infection, but tracheostomy is not usually needed. In this scenario the airway is not severely compromised and in most cases no treatment is necessary, especially if the stenosis is congenital and therefore it is expected to enlarge as the child grows.

When dealing with a symptomatic child requiring treatment, once the whole diagnostic algorithm has been followed, the decision-making should be discussed among the multidisciplinary airway team in order to reach a consensus for the best timing and type of surgery.

Monnier proposed a list of queries that the laryngotracheal stenosis board team should address so as to make the best treatment choice (2):

1. What type of surgery should be appropriate?

a. Endoscopic, LTR, PCTR or extended PCTR?
b. Which type of grafting if needed?

2. Single-stage or double-stage surgery?

a. With or without stenting?
b. Need for intensive care unit?

3. What type and risk of complications to expect?

a. PCTR: anastomotic dehiscence and/or RLN injury
b. LTR: high recurrence rate for grade III-IV subglottic stenosis

4. Which kind of results can be predicted about airway, voice and deglutition?
5. Have all relevant comorbidities been studied?

a. GOR disease?
b. Neurologic, pulmonary and cardiac diseases?
c. Nutritional status?
d. Airway infection or contamination?

6. Is surgical timing appropriate?

a. Maturity of the stenosis?
b. Patient's age and comorbidities?

7. Does the theoretically best surgical procedure fit with the child's comorbidities or other airway abnormalities?

We propose our decision-making flow chart (**Figure 9**) since there is a broad number of treatment options and it is the task of the multidisciplinary team to establish which is the best for each individual patient while keeping in mind the aforementioned issues. Moreover, choosing the correct treatment modality at the very beginning is of paramount importance, otherwise the success of the entire treatment could be compromised.

AUTHOR CONTRIBUTIONS

Material preparation and literature search were performed by MF, FMa, and FMi. The first draft of the manuscript was written by MF, FMa, and FMi. GP and FC reviewed the manuscript. All authors contributed to the study conception and design, read, and approved the final manuscript.

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frontiers in Pediatrics

CASE REPORT
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Recurrent Wheezing in Pre-school Age: Not Only Airway Reactivity!

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Background: About a fifth of all mediastinal masses are primary cysts arising in the absence of other underlying pathology. Bronchogenic cysts, although rare, are the most frequent type responsible for lower airways compression as they often develop in the peripheral branches of the tracheobronchial tree.

Case presentation: We report the case of a 6-months-old child admitted for acute respiratory distress and wheezing not responsive to asthma treatment. Digestive and airway endoscopy proved a mild and a marked reduction of the esophageal and tracheal lumen, respectively. The nocturnal polygraphy showed an underlying obstructive disorder and the chest CT scan confirmed the presence of a wide mediastinal cyst compressing the trachea. The mass, later identified as a bronchogenic cyst, was surgically removed with complete resolution of the patient's respiratory symptoms.

Discussion: Our case shows that differential diagnosis of wheezing in pre-school aged children should encompass causes others than airway reactivity, thus prompting further evaluation and management.

Keywords: pediatrics, wheezing, asthmatic bronchitis, bronchogenic cyst, airways abnormalities

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BACKGROUND

Despite being one of the most common finding in infants and children, wheezing never ceased to be an alarming symptom for both the parents and the physician. It consists of a continuous sound heard during normal expiration or inspiration when airways obstruction is severe (1). A wheezing sound is usually caused by turbulent airflow passing through a narrowed medium-sized airway. Particularly under pre-school age (<6 years), a heterogeneous group of diseases, ranging from a self-limited viral process to a life-threatening disease, can be responsible for this symptom (2, 3). Diagnosis and treatment of young children with wheezing can thus be challenging and assessment of any kind of wheezing should always include a careful examination and detailed medical history, comprising the time of onset and the concurrent clinical manifestations (**Figure 1**). A chronic wheezing unresponsive to any treatment should prompt further evaluation with advanced imaging as to exclude congenital anomalies of the tracheobronchial tree, comprising vascular rings and slings (4), or a mediastinal mass (**Table 1**). We discuss the case of an infant with persistent wheezing and acute respiratory failure due to a large mediastinal mass compressing the lower airways.

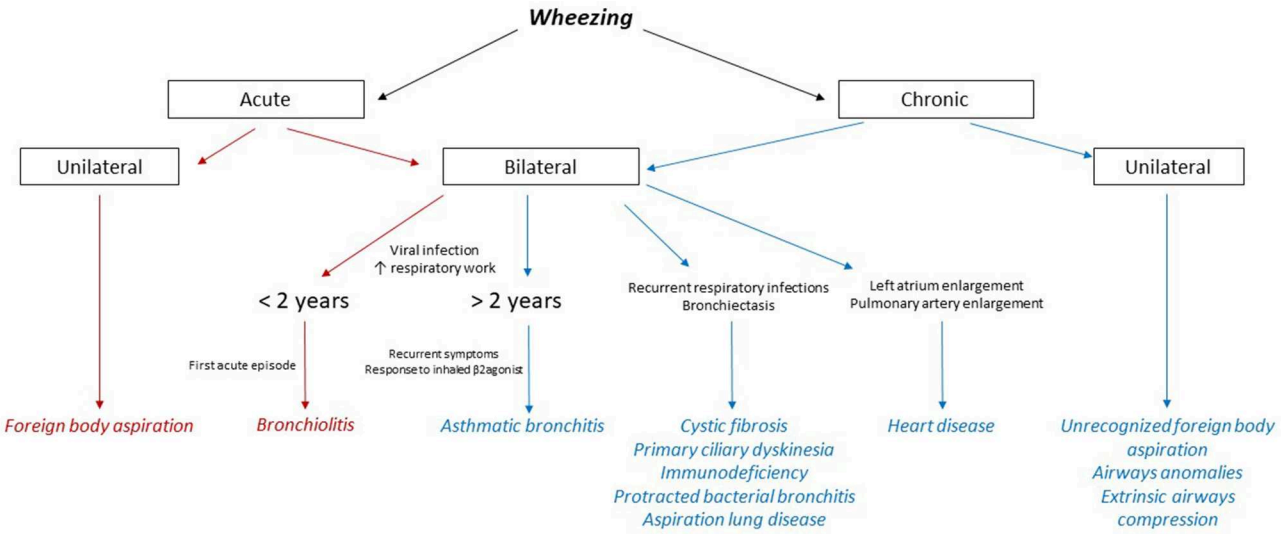

FIGURE 1 | Flow chart on differential diagnosis of wheezing in children. The main causes of acute wheezing are highlighted in red, whereas the conditions underlying a chronic wheezing are colored in blue.

TABLE 1 | Causes of recurrent/chronic wheezing in children.

Tracheo-bronchomalacia*
Vascular compression/rings*
Tracheal stenosis/web*
Extrinsic compression of trachea-bronchial tree (cyst or tumor, lymphadenopathy, cardiomegaly)
Asthma
Gastroesophageal reflux, aspiration
Not recognized foreign body
Bronchopulmonary dysplasia
Cystic fibrosis
Primary ciliary dyskinesia
Immunodeficiency
Bronchiolitis obliterans

These alterations tend to be present in pre-school aged children.

CASE PRESENTATION

A 6-months-old child was admitted at our hospital for acute respiratory failure. Her family history was positive for atopy. She was born at term from a vaginal birth and an uncomplicated pregnancy. Weight at birth was 2,790 g and respiratory distress in the immediate perinatal period was not reported. Recurrent asthmatic bronchitis not responsive to short course of inhaler bronchodilator and corticosteroids and growth retardation without clear symptoms of dysphagia (inability to swallow, regurgitation, gagging, cough during feeding) had occurred in the previous months. The parents reported a progressive worsening of the respiratory load. Physical examination showed dyspnoea, polypnea, prolonged expiration and wheezing worsening while eating. Chest X-ray revealed a normal tracheal air column and main stem bronchi with diffuse thickening of the bronchial walls, as for a non-specific inflammation of the bronchi and their surroundings. Blood tests and microbiologic analysis on respiratory secretions were negative. The echocardiography was limited by a poor acoustic window (due to significant air trapping) and was inconclusive for vascular rings. Based on the history of recurrent symptoms partially responsive to inhaler short term β2 agonists, the patient underwent airway and digestive endoscopy, which revealed a severe tracheomalacia at the T2-T3 level. Antero-posterior compression with a 1:1 ratio between the cartilage rings and the pars membranacea was observed. Anteriorly, the trachea appeared to be compressed by a pulsating mass. No abnormal communications between the airways and the digestive tract were found. Given the airway compression, a nocturnal polygraphy with overnight oximetry was carried out and proved the underlying obstructive disorder. In order to define the extrinsic compression and quantify the tracheal collapse, a dynamic chest CT scan with contrast enhancement was carried out and revealed a 4.0 cm wide mediastinal mass closely adherent to the anterior profiles of the first five thoracic vertebra, both compressing and dislocating the trachea and esophagus to the front and to the right, respectively (**Figures 2A,B**). Integration with ultrasound imaging directed at the jugulum confirmed the presence of a thin walled anechoic cyst. The patient underwent median sternotomy followed by opening of the pericardium and lateralization of the great vessels; total thymectomy was also made necessary to access the mass. On lowering the right pulmonary artery, the voluminous mass was appreciated, tightly adherent to the pars membranacea of the trachea and easily detachable from the esophagus. The cyst, filled with clear liquid and not communicating with the foregut, was therefore punched to reduce its size and facilitate dissection. Histopathological analysis later identified a cystic formation covered by respiratory epithelium and without smooth muscle in the walls, namely a bronchogenic cyst. The postoperative endoscopy revealed complete resolution of the tracheal compression at the T2-T3

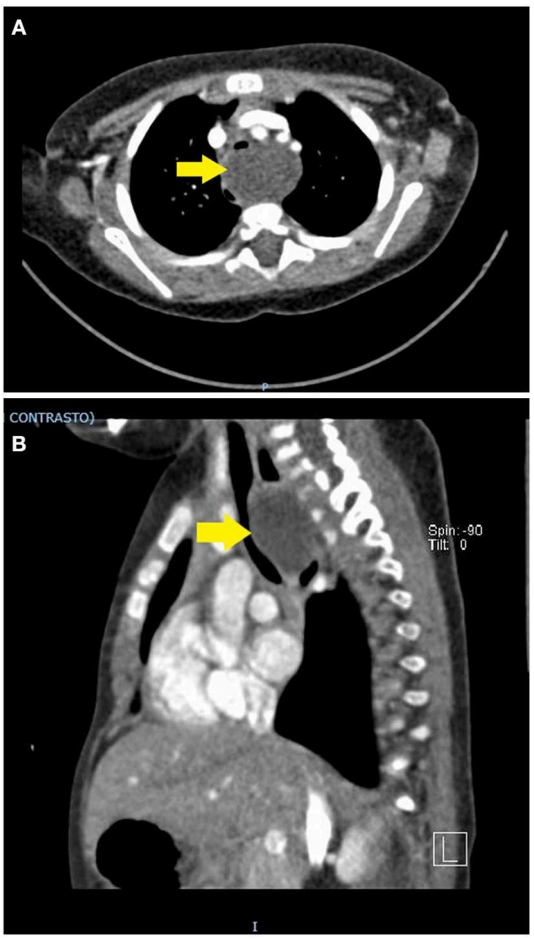

FIGURE 2 | (A,B) Contrast-enhanced chest CT scan. A thin-walled round mass (antero-posterior to lateral diameter, size 30 × 25 × 40 mm) can be seen at the level of the first five dorsal vertebral somas (from D1 to D5). The mass (yellow arrow) occupies the upper and middle mediastinum, displacing the esophagus posteriorly and the trachea anteriorly. In dynamic acquisitions a marked reduction in the size of the trachea to the middle third is documented. The epiaortic vessels appear to be slightly displaced anteriorly without reduction in size.

level. Unfortunately, the patient had a severe respiratory distress with low oxygen saturation, requiring non-invasive ventilation in the intensive care unit (ICU) on the third postoperative day. Both wet and dry crackles could be heard at the right lower lobe. The chest X-ray confirmed the presence of a shaded consolidation at the right lower lobe, consistent with the expected postoperative dysventilation. An urgent endoscopy was required and proved the absence of any fistulous communication between airways and esophagus. Nevertheless, a paralysis of the left vocal cord was detected. Molecular analysis of the sputum later identified an infection by Rhinovirus. The patient respiratory function and imaging gradually improved until she was weaned from ventilatory support. She was discharged 3 weeks after surgery, with only residual expiratory sounds and dysphonia due to the left vocal cord paralysis. One month later, the patient's wheezing completely resolved, and the dysphonia also improved. We obtained informed written consent from the patient's parent authorizing publication of the clinical case and radiologic images. Her anonymity has been preserved.

DISCUSSION

About 20% of mediastinal masses are primary cysts arising in the absence of other underlying pathology (5). Unless they are of unspecified nature, primary cysts can originate from thymus, pericardium, digestive tract and airway system, with the latter being the most frequent type (6). Bronchogenic cysts arise from the precursor of the tracheobronchial tree, the respiratory diverticulum, as proven by their usual location proximal to the trachea or bronchi, either within the lung parenchyma or the mediastinum. In infants, they account for 10% of mediastinal masses and are more common in males (7). The cysts are usually identified by contrast-enhanced chest CT scan as well-defined homogeneous masses adjacent to the lower airways. Two thirds of bronchogenic cysts are asymptomatic, but surgical excision is always necessary as to confirm the diagnosis and rule out malignancies (6). Cyst resection is mandatory in children, even when asymptomatic, as they have a high risk of developing acute respiratory failure later in life, due to compression either of the trachea or bronchi (5). Furthermore, some cases show that half of the patients with bronchogenic cysts may develop complications, such as compression of adjacent structures, infection through a bronchial communication, and rupture into the trachea, the pericardial cavity, or the pleural cavity (8). Other complications of bronchogenic cysts are pneumothorax and pleuritis (9). In our case a common viral infection complicated a difficult postoperative course, given the age of the patient and the size of the cyst that had been removed. The kind of surgery that had been performed also had an intrinsic risk of causing iatrogenic tracheoesophageal fistula (10), thus making frequent endoscopic controls mandatory.

Despite the usual location of bronchogenic cysts within the mediastinum, the given one was well above the carina, compressing both the trachea and esophagus and leading to wheezing without feeding problems. On the basis of cyst's dimension, the symptoms were expected to appear earlier in life, but in our case no respiratory distress was noted at birth or immediately after. Treatment of mediastinal masses, such as the cyst we encountered, is hazardous and should always be managed by a multidisciplinary team. Along with bronchogenic cysts, there are a variety of causes of extrinsic compression of the trachea that may cause wheezing and mimic an asthmatic bronchitis in children, ranging from the more common mediastinal neoplasms to the less frequent vascular rings (11). Therefore, other causes than pre-school asthma have to be taken into account in younger children with wheezing poorly responsive to medical treatment. That is, not all pre-school wheezing means airway reactivity!

ETHICS STATEMENT

We obtained informed written consent from the patient's parent authorizing publication of clinical case and radiologic imagings.

AUTHOR CONTRIBUTIONS

MR made data analysis, wrote the paper and approved the final manuscript. FP contributed to the writing of the paper, revised and approved the final manuscript. PF analyzed the bioptical specimen and made the final diagnosis, revised the paper and approved the final manuscript. AC performed the surgical removal of the cyst, revised the paper and approved the final manuscript. RC contributed to design, revised and approved the final manuscript.

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SYSTEMATIC REVIEW
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Ongoing Laryngeal Stenosis: Conservative Management and Alternatives to Tracheostomy

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Background: Following tracheal intubation, some children may develop stridor, which is an indication of an obstructive lesion in the airway, such as an ongoing laryngeal stenosis (LS). This review focuses on evaluation of stridor and possible endoscopic predictors of progression to LS and, once post-intubation acute lesions are established, therapeutic choices to manage this disorder in avoidance of tracheostomy. Tracheostomy, due to its inherent increased morbidity, mortality and influence on social stigma, should be viewed only as a last resort. In this article, available conservative and alternative therapies for ongoing LS are thoroughly reviewed.

Methods: A systematic review concerning randomized clinical trials and prospective studies on treatment modalities for LS was performed. A search strategy was developed for MEDLINE comprising terms related to disease, intervention and population. Title and abstract from captured references were peer-reviewed for eligibility. Selected studies full-texts were peer-reviewed and the results were compiled in a structured and narrative review. Stridor evaluation and post-extubation acute lesion classification were studied. Treatments such as balloon dilation, rigid dilation, corticosteroid-coated small tube intubation, and corticosteroid nebulization were described and evidence supporting their usage was discussed.

Keywords: airway stenosis, larynx, acute lesions, intubation, laryngoplasty

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INTRODUCTION

Laryngeal stenosis occurs mainly as a consequence of endotracheal intubation. Endotracheal tube induced mucosal injury is a well-recognized etiopathogenic factor leading to stenosis but contributing factors are still a matter of debate. Among these, sedation level (1) and length of intubation (2) have already been demonstrated as definite risk factors.

Definition of acute lesions comprises those identified in <30 days since extubation (3, 4). Moderate to severe lesions pose the highest probability of progressing to chronic stenosis. Recently a classification for acute lesions was proposed with high sensitivity and specificity for the development of laryngeal stenosis. This classification is showed in **Table 1** (5).

Endoscopic treatment of acute lesions may avoid eventual tracheostomy and need for open surgery; or result in a less obstructive lesion that may present a better probability of success for a following intervention.

A range of different endoscopic approaches can be used, both isolated or combined. The use of endoscopic treatment is resurging and this can be attributed to the availability of new and

TABLE 1 | Classification of acute laryngeal Injuries (CALI) as mild, moderate, or severe, according to anatomical location and type of injury.

	Group 1	Group 2	
	Mild	**Moderate**	**Severe**
Supraglottis	■ Edema ■ Hyperemia		
Glottis	■ Edema ■ Hyperemia	■ Uni- or bilateral ulceration ■ Arytenoid GT	■ Inter-arytenoid ulceration ■ Inter-arytenoid GT ■ Immobility
Subglottis	■ Edema ■ Hyperemia	■ Partial ulceration (<360°)	■ Complete ulceration (3,600) ■ GT

GT, granulation tissue.

more sophisticated endoscopic instrumentation and the adjunctive use of new pharmaceuticals (6). Besides, endoscopic treatment results in a shorter operative time, decreased length of hospitalization, avoidance of external incisions, and less emotional and financial burden on the family.

Despite important advances in the management of subglottic stenosis over the last decades, its treatment remains complex and challenging. The aim of this systematic review is to identify current available endoscopic approaches for this disease and evaluate their success rates.

METHODS

Information Sources and Search Strategy

We have performed a comprehensive systematic review in order to identify all reports concerning ongoing laryngeal stenosis and therapeutic strategies. Search strategy was developed for MEDLINE and comprised terms defining laryngeal stenosis and related disorders, and available therapies. Annals from major international meetings in otolaryngology and pediatric airway surgery were also consulted. We have also hand searched references from all retrieved publications and prior systematic reviews. The search strategy for MEDLINE is available in **Table 2**. Further search strategies followed the same structure.

Duplicates were excluded before proceeding to study selection. All titles and abstracts retrieved were screened independently by two researchers. Full-text articles also had its eligibility evaluated by two independent researchers. The last date of the search was July 7th, 2019. We have followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting this study and reporting our results (7, 8).

TABLE 2 | Search strategy for MEDLINE (accessed: 07/07/2019).

Search term	Number of entries
#1: ("Laryngostenosis"[Mesh] OR "laryngeal stenosis"[tw] OR "subglottic stenosis"[tw] OR "laryngeal stenosis"[All fields] OR "subglottic stenosis" [All fields]) OR ("stridor" AND "intubation" [All fields]) OR ("acute laryngeal stenosis" [All fields])	4,192
#2: (Infant[MeSH] OR Infant* OR infancy OR Newborn* OR Baby* OR Babies OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child[MeSH] OR Child* OR Schoolchild* OR School age* OR Preschool* OR Kid or kids OR Toddler* OR Adolescent[MeSH] OR Adoles* OR Teen* OR Boy* OR Girl* OR Minors[MeSH] OR Minors* OR Puberty[MeSH] OR Pubert* OR Pubescen* OR Prepubescen* OR Pediatrics[MeSH] OR Pediatric* OR Pediatric* OR Peadiatric* OR Schools[MeSH] OR Nursery school* OR Kindergar* OR Primary school* OR Secondary school* OR Elementary school* OR High school* OR Highschool*)	4,582,304
#3: (corticosteroid[tw] OR steroid[tw] OR balloon*[tw] OR dilat*[tw] OR rigid*[tw] OR "Mitomycin"[Mesh] OR "1a-docosahexaenoyl mitomycin C" [Supplementary Concept] OR "mitomycin C-N (2)-deoxyguanosine adduct" [Supplementary Concept] OR "mitomycin C-DNA adduct" [Supplementary Concept] OR "mitomycin C-immunoglobulin M antibody conjugate" [Supplementary Concept] OR "mitomycin C-dextran" [Supplementary Concept] OR "mitomycin C-anti-alpha-fetoprotein antibody conjugate" [Supplementary Concept] OR mitomycin[tw] OR "cricoid split"[tw])	543,280
#1 AND **#2** AND **#3**	428

Eligibility Criteria

Inclusion Criteria

We have included all references concerning randomized clinical trials (RCT), phase I and II prospective studies, case series and case reports, involving neonatal (0–28 days old) and pediatric (29 days to 18 years) patients, and reporting results on pharmacologic and endoscopic treatments as primary approaches for ongoing laryngeal stenosis. Only reports in English, Portuguese, Spanish, Italian and German were eligible.

Exclusion Criteria

We have not included other types of publications such as reviews, editorials, letters to the editor, guidelines, study protocols or position papers. All open surgical approaches (even if endoscopic procedures were performed as adjunctive treatment) were excluded. Also, studies pertaining to population samples concerning adult patients (both exclusively or alongside pediatric patients) were excluded. Congenital stenosis or those acquired by other causes not associated with endotracheal intubation were excluded because they do not share the same pathologic mechanisms.

Study Selection and Review

Two reviewers participated in the screening and full-text evaluation. All abstracts screened and articles selected were reviewed by the same two reviewers, while a third reviewer would intervene if there was any discordance over eligibility. Reports were classified based on their main focus, whether diagnosis, prognosis, treatment and complications. All reviews were proceeded independently, and final drafts from both reviewers were eventually compiled into one final review article.

RESULTS

Search Results

The initial search resulted in 432 references. After excluding duplicates and articles not concerning study's population and/or intervention, 106 were eventually assessed as full text. Finally, 22 articles fulfilled eligibility criteria and were included in qualitative synthesis. No quantitative meta-analysis of data was possible due to heterogeneity of interventions and scarcity of comparative trials. Studies content was summarized below. PRISMA flow diagram is depicted in **Figure 1**.

Elective Endotracheal Intubation

Hoeve et al. described 23 patients with a mean age of 37 days who presented extubation failure due to acute laryngeal lesion. They were re-intubated with a "loose fit" tube (inferior in diameter to what would be recommended concerning patient age, permitting leakage of air at the end of an insufflation) for a period of 17 days. Only one of these patients progressed to tracheostomy. When the airway finding was edema or superficial lesions, mean time for intubation was only 8 days and more than half of these patients were extubated within 3 days. When ulceration and edema was found, the mean intubation time was 13 days. However, when granulation was present, intubation longed for weeks afterwards (9).

Graham reported 10 newborn patients undergoing a protocol of 2 weeks of intubation after extubation failure due to acute lesion. Six patients were successfully extubated; two were tracheostomized and decannulated afterwards, with no need for further surgical procedures; one underwent tracheal reconstruction; and the other tracheostomized patient died due to other causes (10).

Monnier recommends that, when dealing with soft-tissue stenosis without mucosal necrosis, a re-intubation should be performed with a one-size smaller endotracheal tube with topical application of an endolaryngeal plug of gentamycin-corticosteroid ointment. Most of these patients can be extubated after a mean re-intubation period of 2–4 days (11).

Endoscopic Balloon Dilation (EBD)

Balloon dilation was first described in 1984 as a method to treat tracheal and bronchial stenosis (12) Subsequently, other case reports were published (13–15). All of them, however, applied balloon dilation for patients with chronic stenoses. The analysis of balloon dilation results for chronic and acute stenoses as separate diseases was only recently attempted.

Compared to previous methods of dilation such as bougies and endotracheal tubes, this new technique has the theoretical advantage of exerting radial pressure on the airway, which projects the stenosis away from the center of the airway, reducing the incidence of shear-related trauma of the epithelium that may occur with rigid dilation (16). Balloon dilation has been studied in several case series since 1991, but its indications, safety and efficacy were still under debate.

The literature search identified 24 abstracts about balloon dilation. After review of the full-length articles, 14 were excluded, due to its use for chronic stenoses (15, 17–20), due to its lack of differentiation between acute or chronic stenosis (16, 19, 21–27), and/or because the paper did not differentiate between rigid or balloon dilations (27, 28). The 10 remaining papers were selected for this review (3, 29–37).

Technique

Balloon dilation is performed under general anesthesia in all articles, using a high pressure, non-compliant balloon catheter. The technique has a slight variability in the studies.

Some authors used the INSPIRA AIRTM balloon (Acclarent Inc., CA, U.S.A.) (33, 37). Other authors do not mention the brands of their balloons and/or use many different brands (3, 29–32, 34–36). The balloon size was selected according to the ideal subglottic diameter for the patient's age (3, 29, 32–34, 36, 37). An inflation/deflation handle mounted with a syringe and gauge assembly designed to monitor and maintain the pressure was used by all authors (29–38). The balloon was inflated to rated burst pressure by some authors (33, 36, 37). Other authors specifically mentioned pressures between 2 and 15 atm, (3) 2 atm, (29, 31, 34), 4 atm, (32), 7 atm (30). The balloon was maintained inflated for 30–60 s or until the patient's oxygen saturation level dropped below 90–92% (3, 29–37). Some authors repeated the procedure 2–3 times during each session (31–37).

Outcomes of Balloon Dilation

The 10 case reports and series (nine retrospectives, one prospective), published between 2007 and 2017, included 109 pediatric patients who underwent 1–6 dilations each, with an average 1.8 dilations per patient. Follow-up ranged from 5 days to 7 years (3, 29–37). Included studies are summarized on **Table 3**.

Success was defined as an improvement of symptoms, decrease in Myer-Cotton level of stenosis, decannulation of previous tracheostomy, or avoidance of reconstructive surgeries and tracheostomy in all studies. Success rate ranged from 66 to 100%, with a total of 97 of the 109 patients (88.99%) reaching a successful outcome.

None of the studies described complications of the procedure. Avelino et al. described that four patients presented dysphagia in the post-operative period, but they do not specify whether these patients had previous acute or chronic SGS (3).

Balloon Adjunctive Treatments

Mitomycin-C

Mitomycin-C is an antibiotic produced by *Strepnomyces caespitosus* exhibiting antiproliferative and antineoplastic properties. It inhibits fibroblast proliferation and synthesis of extracellular matrix proteins, and thereby modulates wound healing and scarring.

Ortiz et al. described 16 children presenting SGS managed with balloon dilation and topical application of mitomycin solution 1 mg/mL in the dilated area for 1 min, reporting a 100% success rate. Authors describe that laryngoscopy was performed as soon as symptoms appeared, but do not specify the time interval between extubation and examination. Mean number of dilation procedures was 2.5, and the number of sessions was proportional to the grade of stenosis (39).

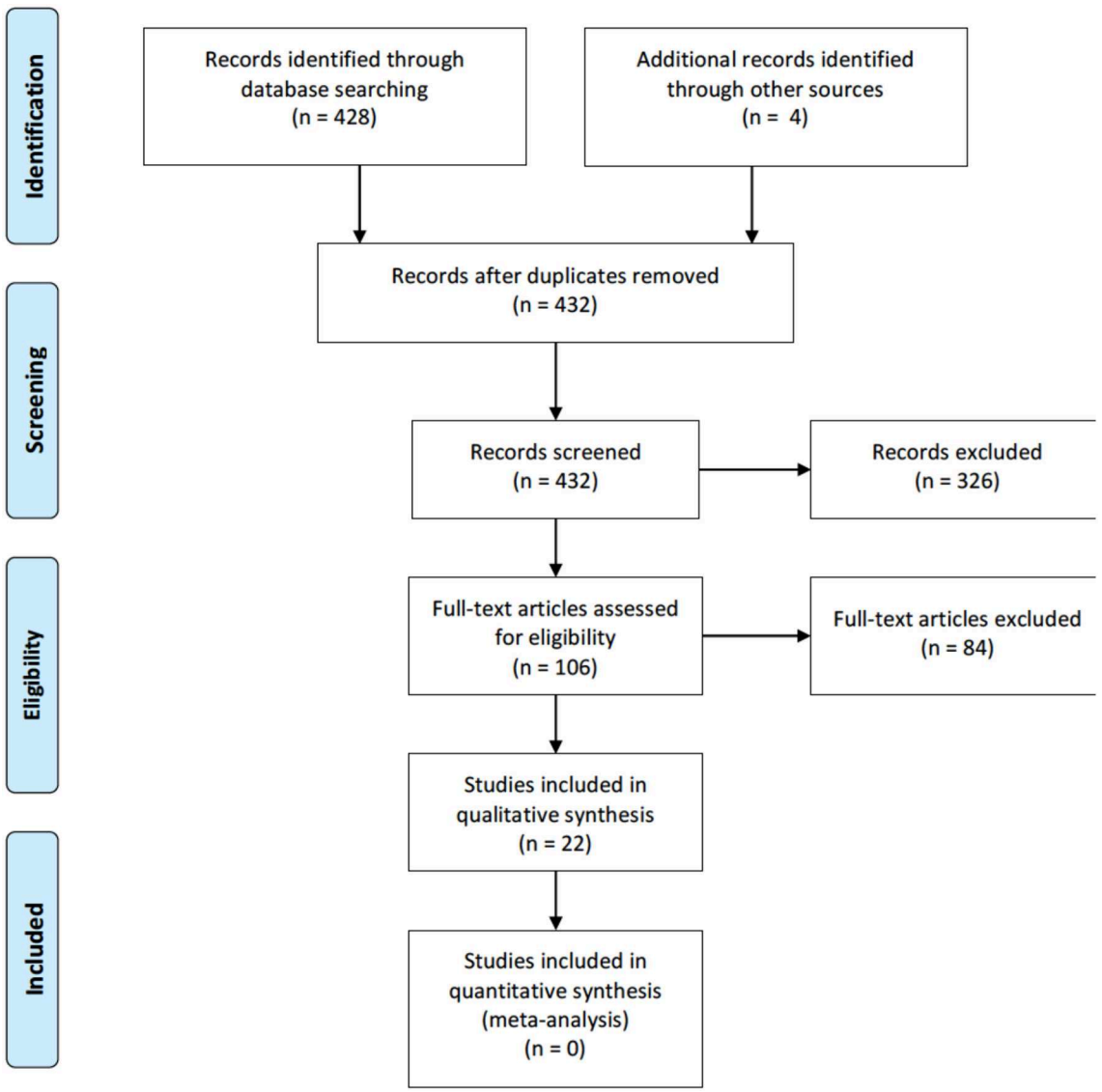

FIGURE 1 | PRISMA flow diagram.

Endoscopic Anterior Cricoid Split (EACS)

Open surgical approach was first described by Cotton as an alternative to performing tracheotomy in premature infants with prolonged intubation. As the aim of the present review is conservative treatments, only EACS is reviewed.

Mirabile et al. (40) described for the first time EBD-associated EACS. They reported five acquired stenosis patients without tracheostomy in whom a 100% success rate was attained. After this first study, Chen et al. (36) described three children presenting acute SGS undergoing EBD + EACS with a success rate of 66.7%. Similarly, Horn et al. (41) described success with the technique in two out of three children presenting extubation failure. Carr et al. (42) described a 100% success rate in five intubated children with extubation failure, using this same approach.

Rigid Dilation

The literature search identified 14 abstracts about rigid dilation. After review of the full-length articles, only one of those studies clearly separated acute and chronic lesion groups, which was eventually included (4).

Dilations were performed with increasing diameter endotracheal tubes, depending on the patient's age. Dilation was started with Silastic (a portmanteau of "silicone"and "plastic") bougies when stenosis prevented the introduction of a 2.5 mm endotracheal tubes. In 12 patients, adjuvant treatment was administered locally, but authors did not separate groups (acute or chronic) for this intervention. Success rate was 96.4% (27/28) and researchers determined that acute stenosis was a predictor of success, while chronic stenosis showed a success rate of 57.1%.

TABLE 3 | Balloon dilation: case reports and case series ($n = 109$).

Author, year. Retrospective X prospective	Number of patients. Age	Description of the type of SGS. Grade of SGS	Number of dilations. Mean number of dilations per patient	Adjuvant treatment	Success rate. Follow-up length
Durden and Sobol (29). Retrospective case series	Four patients. 3–7 mo	Soft. Grades 2–3	1–2 dilations per patient. Mean: 1.2	Topical steroid applied + intubation for 24–48h + systemic steroid	75% success.[a] Mean of 3.5 months of follow-up
Rossetti et al. (30). Retrospective case report	One patient. 10 mo	Acute. Grade 3	1 dilation.	None	100% success. 5 days of follow-up
Schweiger et al. (31). Prospective case series	Eight patients. 2–14 mo	Acute (<60 days after intubation, with GT). Grades 1–3	1–2 dilations per patient. Mean: 1.37 dilations per patient	Systemic steroids	100% success. 6 months of follow-up
Collins et al. (32). Retrospective case series	Two patients.[b] 1 mo (both)	Thin, circumferential SGS. Grade 3	2 dilations. Mean: 1	Topical Mitomycin (1 patient) and topical triamcinolone (1 patient)	100% success. 1–23 months of follow-up
Whigham et al. (33). Retrospective case series	Nine patients.[c] 1–31 mo (mean = 10.8 mo)	Soft. Grade 2–3	14 dilations. Mean: 1.55 per patient	None	66% success. 12–24 months of follow-up
Filiz and Ulualp (34). Retrospective case series	Three patients. 14 weeks-1 yo	Acute (5 days to 6 weeks after extubation). Grades 2–3	3–4 dilations per patient. Mean: 3.33 per patient	Systemic steroids	100% success. 14–21 months of follow-up
Avelino et al. (3). Retrospective	17 patients.[d] Mean: 4.2 mo	Acute (<30 days after extubation). Grades 1–3	Mean: 2 dilations per patient.	Oral prednisolone + steroid nebulization	100% success. 3–15 months of follow-up (mean 7.8 months)
Ozturk et al. (35). Retrospective case report	One patient. 23 days-old	Acute. Grade 3	2 dilations.		100% success. 8 months of follow-up
Alshammari et al. (37). Retrospective	45 patients.[e] 1 mo−15 yo	40 soft, 5 mature. Grades 1–3	1–6 dilations per patient. Mean: 2	1–2 ml Kenalog	82.3% success. 1 year of follow-up
Chen et al. (36). Retrospective	19 patients.[f] 0.3–144 mo (mean = 4 mo)	Acute. Grades 2–4.	1–8 dilations per patient. Mean: 2.6 per patient		100% success. 0.5–7 years of follow-up

mo, months-old; yo, years-old; SGS, subglottic stenosis; GT, granulation tissue.

[a] *One patient in the study needed a tracheostomy.*

[b] *Only patients number two and four were included in this analysis (not clearly described in the paper if the other three patients presented acute or chronic lesions).*

[c] *Only nine patients with soft stenosis and primary balloon dilation (excluded those who underwent adjuvant balloon dilation and those who had firm lesions).*

[d] *Only patients with acute lesions were included in this analysis.*

[e] *Authors described 40 patients with acute lesions and five with chronic ones. They do not separate outcomes of acute and chronic lesions, but since chronic ones accounted for only 12.5% of their patients, it was decided to include all their patients in this analysis.*

[f] *Only patients with acute SGS and who underwent balloon dilation were included in the analysis. Of the 22 patients with acute lesions, three were excluded because they were submitted to balloon dilation + endoscopic anterior cricoid split.*

CO_2 Laser and Coblation

Studies concerning different laser and coblation techniques in laryngeal stenosis deal mainly with chronic stenosis (43–46). Regarding acute lesions, a study by Koufman et al. (47) was found describing five non-tracheostomized patients undergoing stenosis treatment with carbon dioxide (CO_2) surgical laser. Two of them needed tracheostomy, but eventually were decannulated. Dilation and steroid injection were adjunctive measures. Bollig and Gov-Ari (48) described a 9-months-old girl successfully managed with bipolar radiofrequency plasma ablation (coblation) after prior multiple endoscopic balloon dilations.

Microdebrider

Rees et al. (49) described one case of subglottic granulation treated with microdebrider. This was the sole publication reporting the use of this technique in acute lesions.

DISCUSSION

In 1984, Cotton stated that endoscopic techniques were effective in the early phases of wound healing, when the scar tissue is soft and pliable (50). Since then, many techniques have been described, with variable rates of success. Recent technological advances have facilitated endoscopic approaches that promise fewer wound complications, decreased postoperative pain, shortened hospital stays, and no external scarring (40). The success of endoscopic techniques for acute stenosis is defined by the long-term resolution of stenosis and the avoidance of open surgery such as laryngotracheal reconstruction.

Rigid dilations have been used for a long time, with highly variable and essentially disappointing results (51, 52). Rigid dilation studies found in this review do not report clear inclusion criteria especially concerning mature or in evolution stenosis status. Also, miscellaneous etiologies and different age groups were enrolled. Furthermore, reported dilatation techniques and

TABLE 4 | Comparison of therapeutic approaches success rates.

Therapeutic option in acute laryngeal lesions	Success rates*
Elective endotracheal intubation	60 (10)–95.6%(9)
EBD	66 (33)–100% (36)
EBD + mitomycin-C	100% (39)
EBD + EACS	66.7 (36)–100% (40)
Rigid dilation	96.4% (4)
CO_2 laser	60% (47)
Coblation	1 successful case (48)
Microdebrider	1 successful case (49)

EBD, Endoscopic Balloon Dilation; EACS, Endoscopic Anterior Cricoid Split.
**Included studies did not report on complications rates from therapeutic approaches.*

ancillary treatments are heterogeneous. It is known that although this technique is effective, significant sheer forces are generated across the area of stenosis, and ongoing serial dilatations are often required. Studies on rigid dilation showed the need of a high number of repeated dilations but again did not segregate chronic from acute lesions. The only one found stratifying this information reported a mean number of procedures of two and a success rate of 96.4%.

Balloon dilation emerged as a promising alternative to those dilations with bougies, bronchoscopes and endotracheal tubes. It was initially designed for endovascular interventions and later adapted for use in tracheobronchial stenoses by interventional radiologists and pediatric surgeons (12, 13). The absence of shearing forces minimizes subglottic trauma, both at the mucosal level and in deeper planes, thereby decreasing the tendency to re-stenosis. As with conventional dilation techniques, balloon dilation is more likely to succeed in the presence of immature scar tissue (15).

While the number of reports on balloon dilation is still currently small, encouraging reports of this simple technique suggest that balloon dilation is probably the single most promising treatment for acute subglottic stenosis.

There is very little information available in the literature to guide balloon sizing, inflation pressure and length of inflation time. Currently, surgeons often use their own breadth of experience to guide the parameters used in the procedure. Excessively high inflation pressures or big balloon sizes can damage or rupture the airway, and inadequately low pressures or small balloon sizes can reduce the effectiveness of procedures and result in the requirement for even more procedures.

Lee et al. (28) was excluded of the balloon dilation analysis, but interestingly its results showed that, independently of the kind of therapy (bougination, incision using cold knife or laser, and balloon dilation), the success rate for acute SGS (within 30 days after extubation) is 88.8%, compared to 9.09% for chronic stenosis (more than 30 days after extubation). Their success rate sharply equals the success rate of this systematic review (88.99%). In the discussion, authors mention that the success rate is probably related to the SGS grade and nature of the scar tissue, since fine membranous scars and acute membranous type of SGS (immature scar tissue) can be expanded more easily than total cartilaginous fibrosis (mature scar tissue).

However, since the outcome of the dilation was not 100% in many studies, adjuvant therapies, such as steroid local injection, systemic steroids have been added to the therapeutic options in some cases. As we could notice in this systematic review, evidences about these adjuvant therapies are scarce. Also concerning other approaches such as CO_2 laser, coblation and microdebridor, further studies are necessary in acute lesions to settle debate over those specific treatments.

The establishment of endoscopic management protocols is complex due to technique variability and multiplicity among different institutions and patient's individual characteristics. Success of endoscopic treatment is probably also significantly influenced by the skill and ability of the collaborative staff, especially anesthesiologists and neonatal/pediatric critical care specialists. **Table 4** summarizes success rates from therapeutic approaches discussed in this review.

As far as authors are concerned, if the acute lesion is restricted to subglottis, EBD is the best option. In the postoperative period, steroid nebulization and proton pump inhibitor use has become a promising adjuvant treatment. Review laryngoscopy around the seventh postoperative day should always be performed, or even earlier if symptoms become noticeable. Procedure may be repeated many times, as long as the subglottic lumen is improving with each dilation. If the lumen is still not good enough after the second dilation, adjuvant treatment as topic steroids are advisable. Authors do not recommend more than 4 dilations–if the patient would require more than 4 dilations, it seems reasonable to change the therapeutic approach. When there is an associated glottic lesion or widespread airway edema or granulation tissue, reintubation with a one-or two-size smaller endotracheal tube with topical application of a steroid ointment for 48–72 h seems to be an attractive approach. Soon after extubation, we also recommend the use of inhaled corticosteroid and proton pump inhibitor.

Future studies should examine the effects of different balloon diameters and pressures, the role of adjuvant therapies such as steroid local injections and systemic steroids, and also the difference between rigid and balloon dilation. There are currently no evidence-based guidelines for the treatment of post-intubation acute laryngeal lesions, and the clinical experience of each team often guides the therapeutic approach.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

CS and DM participated in study design, search strategy elaboration, peer-review, narrative review, manuscript writing, and final revision.

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CASE REPORT
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The Important Role of Endoscopy in Management of Pediatric Pseudomembranous Necrotizing Tracheitis

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Pseudomembranous necrotizing tracheitis is a rare, but life-threatening cause of central airway obstruction. Here, we reported three cases of pediatric pseudomembranous necrotizing tracheitis. The infectious etiologies were *Staphylococcus aureus* secondary to influenza A virus *and Aspergillus fumigatus*. Endoscopy was used in diagnosis and management of all patients and two patients survived. The improvement in mortality rate of these diseases need early recognition and prompt treatment with mechanical debridement by endoscope and early initiation of broad spectrum antibiotics. Endoscopy is a promising tool to diagnose and remove the pseudomembrane, therefore relieving central airway obstruction.

Keywords: necrotizing tracheitis, endoscopy, airway obstruction, mechanical debridement, pediatric

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INTRODUCTION

Pseudomembranous necrotizing tracheitis is a rare, but life-threatening cause of central airway obstruction. Common infectious etiologies included bacterial, fungal, and/or viral infection(s) (1). The risk fact was bacterial infection secondary to influenza virus and long-term use of hormones or antibiotics. Patients usually have hoarseness, cough, dyspnea, wheezing and inspiratory stridor. Diagnosis requires a comprehensive endoscopic examination and biopsy (2). Endoscopy (flexible or rigid) has a very important role in both diagnosis and management of pseudomembranous necrotizing tracheitis. Once patients exhibit signs and symptoms of airway obstruction, mechanical debridement by endoscopy is necessary (2). A delay in treatment can significantly worsen the patient's prognosis. Here, we report three cases of pediatric pseudomembranous necrotizing tracheitis. Endoscopy was used to remove the pseudomembrane in all patients and two patients survived.

CASE PRESENTATION

Case 1

A 20-month-old girl presented at our hospital with a history of cough and fever for 2 days, and shortness of breath for 1 day. She also had hoarseness. On admission she was short of breath and exhibited laryngeal stridor. Physical examination revealed that there was no wheezing in both lungs. Computed tomography (CT) demonstrated inflammation in the left lower lobe. Her initial laboratory tests results were as follow: hemoglobin 11.6 g/dL, WBC14.11 $\times$ 10^9 /L, platelet count of 272 $\times$ 10^9 /L, and C-reactive protein (CRP) of 63 mg/L. On the first night of admission, laryngoscope was performed and revealed mucous edema of the larynx. Her situation

deteriorated quickly, subsequently requiring intubation. However, her oxygen saturation was still unstable and the airway pressure was high during mechanical ventilation. She received tracheal tube replacement, during which brown solid matter measuring ∼1 cm was drawn from her trachea (**Figures 1A,B**). After tube replacement, her airway pressure decreased and her situation improved after 2 days of meropenem and methylprednisolone treatment Mechanical ventilation was changed to a face mask. Both WBC count and CRP level subsequently decreased to within normal ranges. Sputum bacterial cultures showed a small amount of methicillin-sensitive *Staphylococcus aureus* (MSSA) grow. Sputum antigen testing of influenza (A and B), parainfluenza (I, II, and III), respiratory syncytial virus, adenovirus was negative, and the tuberculin skin test was non-reactive. On day 4, fiberoptic bronchoscopdy showed substantial white matter attached to the anterior commissure of the larynx and trachea (**Figures 2A1,A2**). Biopsy was performed for pathologic evaluation. Histologic evaluation of biopsy samples revealed flaky necrotic tissue and massive neutrophil infiltration (**Figure 3A**). On day 5, CT showed a slight high-density cord-like image ∼2 cm below the vocal cord and pneumonia in the left lower lobe (**Figure 4A**). Pathogen detection including fungi, viruses, and bacteria was negative.

The patient had cyanosis and shortness of breath after a gust of coughing on the evening of day 6 after admission. Oxygen saturation decreased to 69%. She had convuls after 2 min and her heart rate decreased with oxygen saturation of 60–70%. We performed tracheal intubation and cardiopulmonary resuscitation. X-ray showed pneumothorax in bilateral lungs and the patient died within 3 h.

To further clarify the causative pathogen, DNA from necrotic tissue was extracted using the DNA Extraction Kit (Omega Bio-Tech Co., Ltd) and determined to be positive for *S. aureus* by the *Staphylococcus aureus* Real Time PCR Kit (Shanghai ZJ Bio-Tech Co., Ltd.).

Case 2

A 28-month-old girl was admitted with a history of fever and cough for 4 days and progressive shortness of breath for 3 days. Her sputum was brown. Upon admission, she was short of breath and irritable with positive tri-retraction sign. Bilateral respiratory sounds were decreased with rhonchus. Routine blood routine examination revealed WBC of 11.71 $\times$ 10^9/L and CRP of 93 mg/L. X-ray showed inflammation in bilateral lungs (**Figure 4B**). The patient was hoarseness, shortness of breath, restlessness and the blood gas indicated the decrease of oxygen saturation. She was diagnosed with acute laryngitis with three degrees of laryngeal obstruction, type I respiratory failure, and pneumonia. On the first day of admission, laryngoscopy was performed, which revealed substantial yellowish-white pus in the trachea. Respiratory failure rapidly progressed, subsequently requiring intubation. Bronchoscopy was performed and revealed substantial yellowish-white pus attached to the trachea and right main bronchus (**Figures 2B1,B2**). Biopsy was then performed (**Figure 1C**). Alveolar lavage fluid tests indicated the following: lymphocytes 8%, neutrophils 30%, macrophages 63%, and eosinophils <1%. Histologic evaluation revealed fibrin necrotic exudates (**Figure 3B**). Sputum analysis for viral antigens revealed influenza A positivity. Lavage fluid culture was positive for *S. aureus*. Pathogen detection for fungus or other bacteria was negative. The patient was treated with meropenem, vancomycin, and methylprednisolone. Oseltamivir was also given. Bronchoscopy was performed four times to remove the pseudomembrane and her condition improved. However, on day 8 of admission, her oxygen saturation decreased and she was suspected of having mucous membrane exfoliation. A white sputum bolt sample measuring 2.5 cm was removed by rigid microscopy and the patient's oxygen saturation increased to within normal ranges.

On day 10, the patient's tracheal tube was removed and bronchoscopy was performed seven consecutive times. The tenth bronchoscopic examination showed clear reduction in endotracheal secretion and the mucous membrane was a normal color. On day 32, she was discharged from our hospital.

Case 3

A 19-month-old girl presented at our hospital with a history of recurrent fever and cough for 2 weeks. She was diagnosed

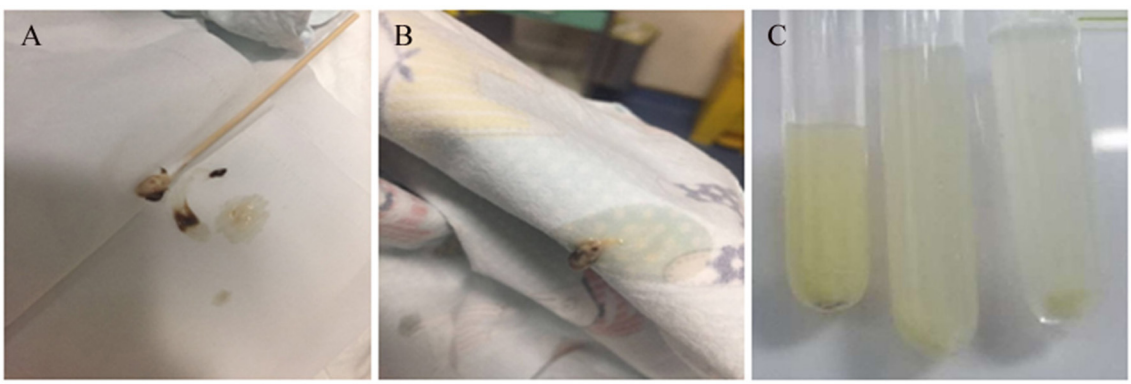

FIGURE 1 | Images of airway secretions or mucous exudates for cases 1 and 2. **(A,B)** Case 1, **(C)** Case 2.

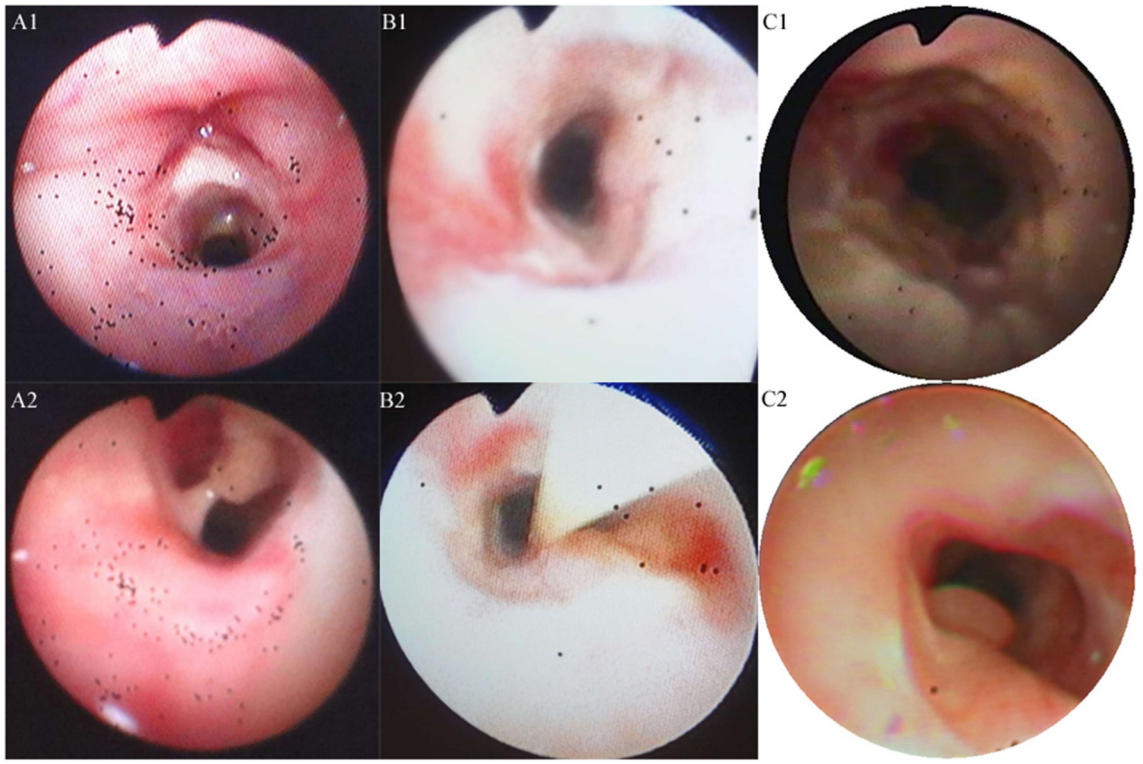

FIGURE 2 | Trancheal bronchoscopy images for the three cases. **(A,B)** Cases 1 **(A1,A2)** and 2 **(B1,B2)** showed substantial purulent secretion and necrotic mucosa. **(C)** Case 3 showed necrotic mucosa during acute phase **(C1)** and irregularly shaped trachea and granulation during the recovery phase **(C2)**.

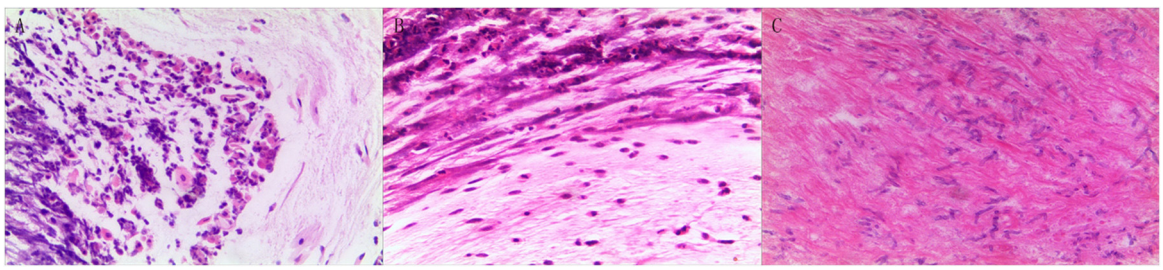

FIGURE 3 | Pathologic results of tracheal biopsy for the three cases. **(A)** Case 1 exhibited neutrophil infiltration and fibrinoid necrosis. **(B)** Case 2, it showed fibrinoid necrosis and purulent cells. **(C)** Case 3 demonstrated fibrinoid exudation and substantial *Aspergillus* load. (Hematoxylin and eosin staining, 200 × magnification).

with pneumia by a local hospital and had received azithromycin, ceftriaxone, and methylprednisolone treatment. However, her fever and cough persisted. Upon admission at our hospital, her respiratory rate was 70 breaths/min and body temperature was 39.7°C. Her eyelids were swollen and she had a needle-like rash over her entire body. Chest examination revealed crackles in two lung fields. Laboratory examinations revealed WBC count of 2.5×10^9/L, normocytic anemia (hemoglobin of 10.1 g/dL), thrombocytosis (platelet count of 75×10^9/L), and elevated CRP of 28 mg/L. CT demonstrated inflammation in the lungs and pleural effusion. We suspected infection by a drug-resistant microorganism and administered imipenem and methylprednisolone therapy. On day 9, her condition deteriorated and her respiratory rate increased with frequent cyanosis. The patient subsequently received tracheal intubation and mechanical ventilation. Because we could not exclude the possibility of methicillin-resistant *S. aureus* (MRSA) infection, vancomycin was administered. However, her oxygen saturation was only about 80%. X-ray showed interstitial emphysema, mediastinal emphysema, and subcutaneous emphysema in the lungs. She then received extracorporeal membrane oxygenation for 5 days. On day 22, bronchoscopy was performed, which revealed substantial purulent secretion and necrotic areas throughout the tracheal mucosa (**Figure 2C1**). Her condition improved and her tracheal tube was removed. Histologic evaluation showed inflammatory necrotic tissue

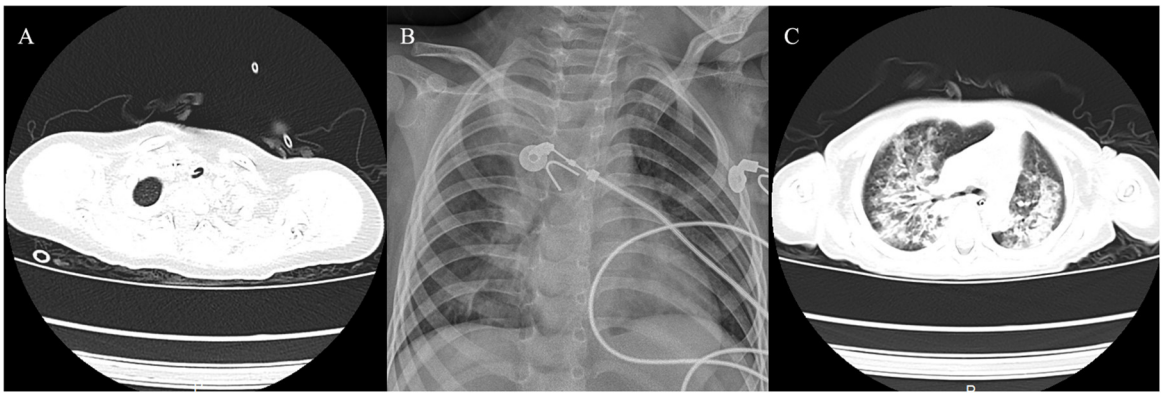

FIGURE 4 | Imaging findings of the three cases. **(A)** Case 1 showed membranous material that was strongly adherent to the tracheal wall. **(B)** Case 2 showed inflammation in bilateral lungs. **(C)** Case 3 had local stenosis of right main bronchus.

and *Aspergillus fumigatus* infection (**Figure 3C**). Repeat CT showed local stenosis of right main bronchus (**Figure 4C**) and a cavity formed near the pleura in the right lower lung. She subsequently received voriconazole, caspofungin, and amphotericin B treatment. Bronchoscopy was performed seven times to remove the pseudomembrane. The last bronchoscopic examination during hospitalization showed tracheal stenosis and granulation (**Figure 2C2**). On day 44, she was discharged from our hospital and received oral voriconazole for 6 months. The last bronchoscopic examination showed persistence of some mucosal irregularities. CT taken 1 year after discharge showed almost complete absence of lung inflammation.

All patients were previously healthy and had no significant family history.

DISCUSSION

Pediatric pseudomembranous necrotizing tracheitis is rare. The disease was first reported as a complication of prolonged assisted ventilation in newborns in 1983 (3). Despite mucosal trauma from mechanical ventilation, mucosal damage from an antecedent viral infection may contribute to the pathogenesis of this disease (4, 5). The most common infectious etiologies reported were *Corynebacterium diphtheria, Corynebacterium pseudodiphtheriticum, S. aureus, Bacillus cereus, Pseudomonas aeruginosa, Aspergillus species, and Haemophilus influenza* (2, 5, 6). Opportunistic infection occurs in immunosuppressed patients such as those with hematologic malignancies, organ transplantation, or neutropenia (7). Pseudomembranous necrotizing tracheitis can also be a rare extra-intestinal manifestation of ulcerative colitis in children (8). This disease should be differentiated from acute laryngitis, epiglottitis, foreign body inhalation, and obstructive fibrinous tracheal pseudomembrane (9).

Bacterial bronchitis primarily affects preschool and early school-aged children, however, cases of children with necrotizing tracheitis are rarely reported (10). We searched the PubMed and Embase databases for articles published until December 30, 2019, using the following search terms: (necrotic OR necrotizing OR pseudomembranous OR aspergillus) AND (tracheitis OR tracheobronchitis). Neonatal necrotizing tracheitis was excluded. We only found seven cases of pediatric necrotizing tracheitis (**Table 1**). The exact incidence is unknown. All cases presented with high fever, cough, inspiratory stridor, hoarseness, and tachypnea. All patients had acute deterioration characterized by severe upper airway obstruction.

In the present report, all patients were girls aged 1–3 years old. The first two patients got ill in the spring, while the third fell ill in the summer. The infectious etiologies of the three cases were MSSA secondary to influenza A virus, and *Aspergillus* sp. However, the mechanism by which these infections progressed to necrotizing tracheitis was not entirely clear. Although community-acquired *S. aureus* strains isolated from the first two patients were sensitive to methicillin, the strains likely had stronger virulence than the typical MSSA strains. Case 2 had coinfection of influenza A virus and *S. aureus*. These organisms are known to have destructive synergism. For instance, *S. aureus* strain was shown to secret proteases capable of enhancing influenza infectivity and pathogenicity in the respiratory tract5. In case 3, Aspergillus infection may have resulted from the patinet's long-term use of antibiotics and hormones, and neutropenia. The course of disease for *Aspergillus* infection is longer and the prognosis is relatively poorer than other etiologies.

Imaging features of pseudomembranous necrotizing tracheitis include circumferential thickening of the trachea, tracheal stenosis, and diffuse haziness and irregularity of the tracheal wall (13). The CT scan of case 1 showed membranous material compatible with endoluminal densities that was strongly adherent to the tracheal wall below the vocal cord. All cases had radiological findings suggestive of pneumonia.

Microscope images can aid in the correct diagnosis of patients with complex respiratory conditions of similar presentation (1, 14). Bronchoscopic findings consisted of membranous plaques, thick respiratory secretions, ulceration, or denudation

TABLE 1 | Cases of children with necrotizing tracheitis.

Number	Age	Sex	Etiology	Basic disease	Imaging	Endoscopic findings	Prognosis	Country	Reference
1	3m	F	Unknown	Tetralogy of Fallot and absent pulmonary valve, a radical cure	Strong stenosis was supposed at the truncus intermedius	The mucosa was red with some scabs and the lumen was narrow with a lot of secretions	Died	Japan	(11)
2	8m	M	Unknown	No	Left lung was hyperinflation with mediastinal shifting	There were swelling, bleeding, necrosis, and scab in tracheal and bronchial mucosa	Well	Portugal	(12)
3	9y	F	Influenza A and methicillin-resistant *staphylococcus aureus*	No	Chest X-ray revealed there was bilateral patchy infiltration	Copious dark and cloudy secretions, ragged, and severely edematous with adherent fibrinous debris and patchy plaques	Died	USA	(13)
4	5y	F	Aspergillosis	Fanconi anemia	CT of the thorax revealed bibasilar pulmonary opacities	A white exophytic lesion was in the tracheal	Died	Colombia	(14)
5	9y	F	Aspergillosis	Chronic myelogenous leukemia,hematopoietic cell transplantation	Chest X-ray was normal. Lateral neck films showed subglottic airway narrowing with soft tissue fullness of the glottis and subglottic areas	There were an erythematous and edematous supraglottis and extensive pseudomembranous and obstructive tracheitis, an estimated 50–60% of the entire tracheal lumen was filled	Died	USA	(15)
6	16y	F	Unknown	Ulcerative colitis	Not mentioned	There were mucous ulceration and white plaques along tracheal	Well	Portugal	(8)
7	7y	F	Influenza A-H1N1 combined with *staphylococcus aureus*	No	Chest X-ray showed there was inflammation in the right lung	There were black and yellow necrotic substances in the main airway, accompanied by hemorrhage and a large amount of yellow purulent substances	Died	China	(16)

of airway mucosa (15). Endoscopy (flexible or rigid) also has an important role in both tracheal and bronchial tissue sampling for microscopic analysis and culture, and helps to avert the need for intubation (17). Treatment in the acute phase of the illness frequently requires insertion of an endotracheal tube into the inflamed airway, which may lead to the subsequent development of mucosal shedding and subglottic stenosis. Once a patient exhibited signs and symptoms of central airway obstruction, he or she often needs immediate bronchoscopic intervention to restore airway patency (2). Rigid bronchoscopy is the safest treatment modality, both for confirming and relieving airway obstruction in patients with acute respiratory failure (18, 19). It can maintain airway open, diagnose quickly and relieve airway obstruction in time. When the patient deteriorated or his vital signs were unstable, rigid bronchoscopy will be the first choice.

Given the concern about early scar formation and recurrent airway obstruction, it has been suggested that early flexible bronchoscopy should be performed in patients with evidence of severe tracheitis (2). In this report, repeated resection of pseudomembranous was often carried out under flexible bronchoscopy.

Case 1 was our first experience of necrotizing tracheitis. The patient only received endoscopic examination twice. When her situation worsened, her parents refused intervention by rigid endoscopy. She subsequently died of profound mucosal sloughing, which almost completely obstructed the main airway. The other two cases received endoscopic examination and mechanical debridement several times and showed a significantly improved prognosis. Therefore, awareness and early recognition and therapeutic intervention are essential to improved prognosis and prevent progression to respiratory failure in pediatric pseudomembrance necrotizing tracheitis.

Broad-spectrum intravenous antibiotic therapy should be initiated as soon as the clinical diagnosis is made. A third-generation cephalosporin agent combined with a beta-lactamase resistant penicillin is appropriate for first-line therapy (20). If MRSA is suspected, then vancomycin or linezolid should be chosen. Antibiotic coverage should also be modified according to culture. Voriconazole is currently the first choice for the treatment of invasive aspergillosis (7). Corticosteroids treatment remains controversial. However, based on the rationale that they reduce airway inflammation and oedema, it was used in most of patients (21).

CONCLUSION

Pseudomembrance necrotizing tracheitis should be considered in children who present with an acute, life-threatening upper airway obstruction. Improvement in the mortality rate of this disease requires early recognition and prompt treatment with mechanical debridement by endoscopy and early initiation of broad-spectrum antibiotic therapy.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZC supervised research work. XW and LW participated in collecting information of three cases and searched for literatures. They contributed equally to this work. All authors participated in the interpretation of the data. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Surgical Management of Anterior Glottic Webs

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Congenital webs are rare and represent <5% of all congenital laryngeal anomalies. They are usually a partial laryngeal atresia rather than a true web, and present as a thick and fibrotic web with subglottic extension and associated subglottic stenosis. All patients with a congenital anterior glottic web should be evaluated for chromosome 22q11.2 deletion syndrome. Management strategies are mainly based on the severity of airway obstruction and the anatomical extension of the webs. Simple division of the web endoscopically may be adequate for rare thin webs, however, an open approach is usually warranted for thick glottic webs regardless of Cohen grades. Open repair can be either with keel placement or reconstruction of the anterior commissure.

Keywords: congenital glottic web, congenital subglottic stenosis, laryngeal keel, laryngeal atresia, anterior commissure

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Laryngeal webs are either acquired or congenital. Congenital webs are uncommon and represent fewer than 5% of congenital laryngeal anomalies. Congenital webs result from a disruption of autolysis of the laryngotracheal groove during 10th week of embryogenesis. Congenital webs vary in size and thickness based on the interruption of the embryologic recanalization process. Therefore, most congenital webs are a form of laryngeal atresia rather than a true web, and present as a thick and fibrotic web with subglottic extension resulting a subglottic stenosis with a small cricoid. In lateral xenography of the airway, the appearance is termed a "subglottic sail" (**Figure 1**). Anterior glottic webs are the most common type and comprise more than 95% of cases (1).

While there is no single defined gene that results in congenital glottic webbing, there is a significant association between anterior glottic webs and chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome and DiGeorge syndrome). Approximately 65% of patients presenting with an anterior glottic web will have chromosome 22q11.2 deletion syndrome (2–5), and as the web may be the only early manifestation, it is recommended to refer all patients with congenital anterior glottic webs for genetic assessment.

Children born with congenital webs always have an abnormal or even absent cry at birth, and may present with airway obstruction, according to the thickness and location of webs. In an infant presenting with significant airway compromise in the first few days of life, the web is likely severe, and will require emergent airway intervention. Infants are remarkably tolerant of congenital airway compromise, and even patients with severe glottic webbing may initially show only mild airway symptoms, which then exacerbate over the first few months of life. Airway symptoms of severe webbing including biphasic stridor and retractions, which exacerbate when upset or feeding. In more severe cases, failure to thrive, apnea, and cyanosis are characteristic.

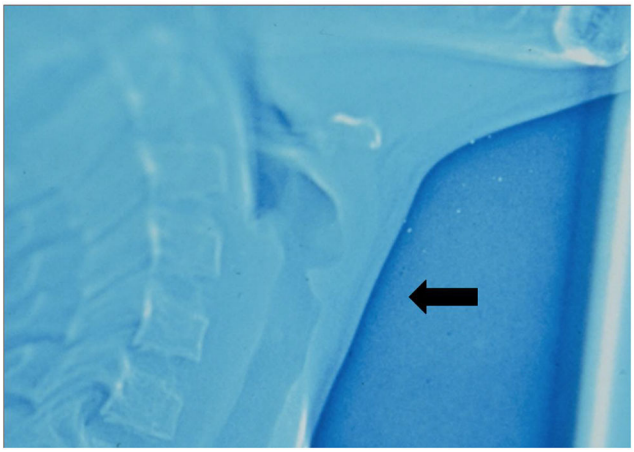

FIGURE 1 | "Subglottic sail" appearance in xenograph.

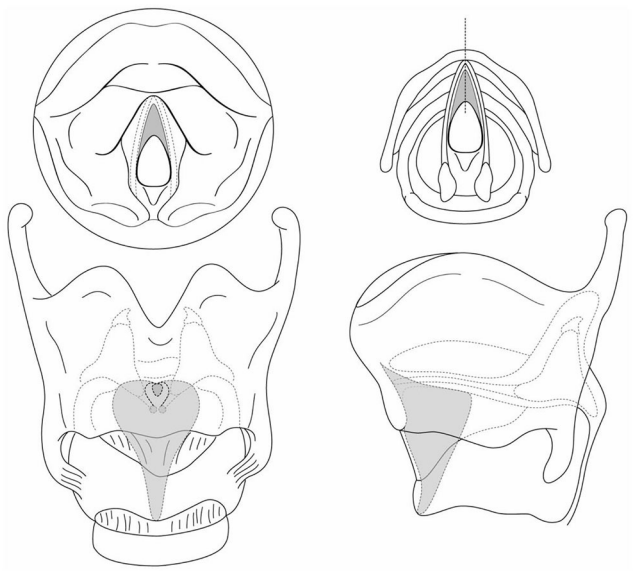

FIGURE 2 | The laryngeal web with subglottic extension appears as a "subglottic sail".

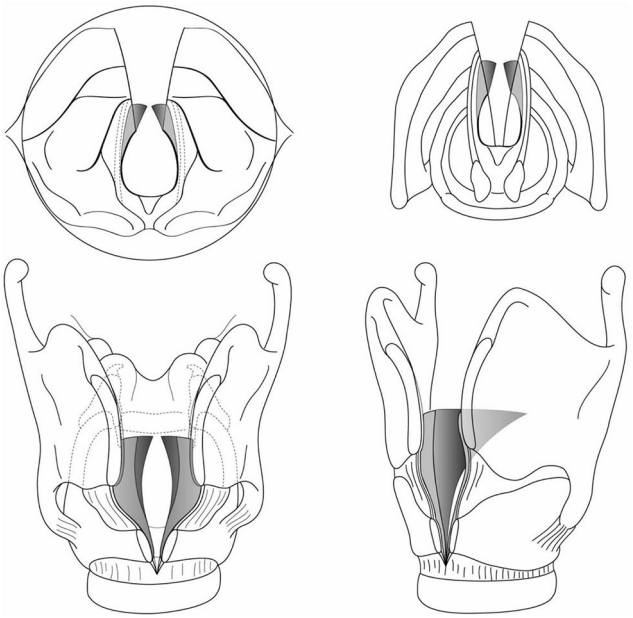

FIGURE 3 | The laryngofissure is down and through the cricoid cartilage.

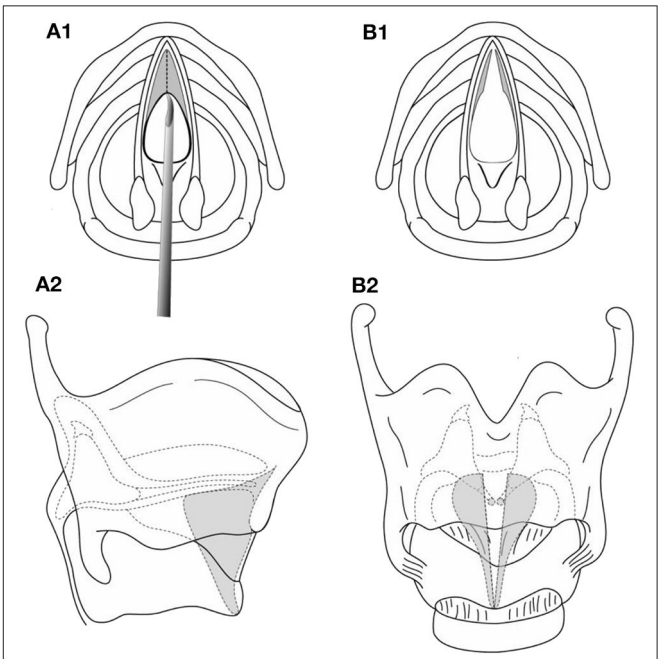

FIGURE 4 | (A1,A2,B1,B2) Endoscopic division of an anterior glottic web.

Initial evaluation should include awake flexible laryngoscopy to excludeother pathologies, such as laryngomalacia or vocal cord palsy. For definitive evaluation rigid bronchoscopy is recommended, with both the severity of the web and its subglottic extension being assessed. Flexible bronchoscopy offers an excellent view of the anterior commissure, and is therefore complimentary; whereas rigid bronchoscopy better evaluates the degree of subglottic stenosis, and angled (70°) telescopes may provide superior images of the web. In children with a severe web, bronchoscopy should be performed with care, to avoid further compromising an already compromised airway, and spontaneous ventilation with the infant maintaining his or her own airway is preferable to intubation or emergent tracheotomy (6).

Management strategies are mainly based on the severity of airway obstruction and the anatomical extension of the webs (7). The anterior glottic webs are classified by the percentage of vocal cord involvement and the presence of subglottic extension which postulated by Cohen (8) in 1985.

According to the Cohen classification, a type 1 glottic web is a thin web with <35% of glottic involvement. Type 2 involves 35∼50% of glottis. A type 3 web, has a 50∼75% glottic involvement with anterior cricoid cartilage extension resulting in subglottic stenosis (SGS) formation. And a type 4 web involves 75∼90% of the glottis with cricoid extension and associated SGS.

Infants with a type 1 web may present no respiratory symptoms but hoarseness whereas type 2 web causes mild airway symptoms and a weak cry. For a rare true gossamer-thin anterior glottic web, it may never be formally diagnosed, as intubation for airway stabilization may lyse the web and completely resolve the problem. In the rare thin type 1 and 2 anterior webs, simple division of the web endoscopically with a cold instrument (ex. sickle knife) is simple and effective, usually with the baby suspended on a small Lindholm laryngoscope. Excision can also be done with CO2 or KTP laser. Topical application of mitomycin-C is aimed to reduce scar formation, but evidence suggests that mitomycin-C may delay instead of preventing restenosis (9). Whereas, for thick glottic webs regardless of Cohen grades, open approach is usually warranted instead of endoscopic methods (10) as these webs have a strong tendency to recur after endoscopic division.

The timing for repair is mainly based on the severity of airway symptoms. For a severely compromised airway, intervention may either be early repair or tracheotomy placement with late repair. For mild or moderate webs without clinical airway compromise, late repair is preferable. A larger larynx makes surgery technically much easier. Late repair is typically performed by age 4 years, to improve voice quality before school age. Repair may be performed as a single- or double-staged procedure, depending on the experience of intensive care facilities and whether a tracheostomy is already present. A double-stage procedure with a suprastomal stent left in for a longer period is usually warranted for more severe subglottic stenosis, and in 22q11.2 deletion syndrome, especially the DiGeorge variant, post-operative edema may be a feature for months.

External approaches can be either reconstruction of the anterior commissure or open keel placement open. Open keel placement is reasonable for a severely scarred web (congenital or acquired) and requires a complete laryngofissure to adequately expose the larynx by splitting the thyroid cartilage under endoscopic guidance for ensuring midline approach. To facilitate meticulous midline placement of the laryngofissure, we recommend partially incising (grooving) the thyroid cartilage between the superior and inferior thyroid notches. When the web involves the subglottis as a "sail" (**Figure 2**) extending to the lower border of the cricoid cartilage, the laryngofissure is carried through the cricoid cartilage (**Figure 3**). To evaluate whether an anterior cartilage graft is required, a segment of age-appropriate endotracheal tube is placed through the split cricoid. If the subglottis cannot close comfortably over the endotracheal tube, a graft is used to repair the associated subglottic stenosis. The graft is inserted at cricoid level with its superior aspect being the upper border of the cricoid cartilage, and an appropriate size laryngeal keel is trimmed and inserted between the upper border of the anterior cricoid graft (if such a graft is present) to the superior thyroid notch. For preventing epiglottic petiole prolapse, the keel should be placed below the petiole insertion.

The infraglottic part of the keel should extend far enough to cover the raw split edges of the web, but should not about the

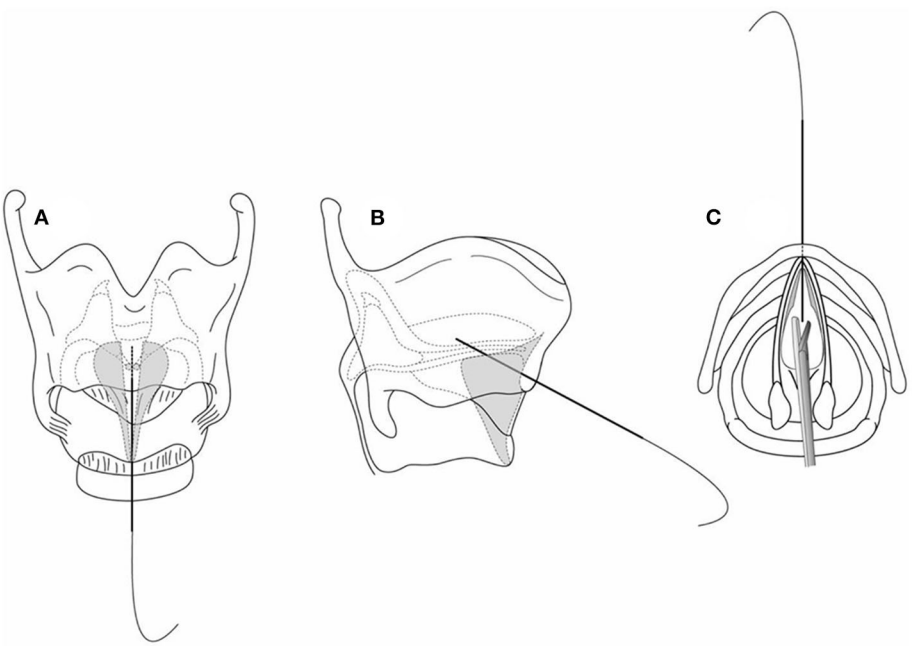

FIGURE 5 | (A–C) The suture to secure the web is passed into the larynx from externally.

mucosa of the posterior glottis. The keel is sutured into place with a complex suture technique. The airway is then closed with either single- or double-stage procedure. The keel is usually removed within 2 weeks, with longer stenting periods used for more severe webs. Another open procedure with laryngofissure is required for stent removal. Laryngofissure closure requires laterally placed mattress sutures.

There is an endoscopic alternative for laryngeal keel placement which is technically more challenging. It is ideal for minor webs whether congenital or acquired. Tracheotomy or intubation may not be necessarily required. This technique involves initially suspending the larynx with a laryngoscope, and endoscopically dividing the web with a sickle knife (**Figure 4**). With the patient still suspended, the neck is then prepped, and a small horizontal incision is made over the thyroid cartilage. A 4.0 Prolene suture on a small straight (Keith) needle is then passed through the midline of the lower thyroid cartilage, below the web, and visualized in the airway. The assistant then grasps the needle with a laparoscopic needle holder, and withdraws the needle from the mouth (**Figure 5**). The surgeon then places a hollow large bore needle through the midline of the upper thyroid cartilage, above the web until it is visualized in the airway. Next, an appropriate laryngeal keel (typically a thin piece of silastic sheet) is used to cover the raw surfaces of the web and passes the straight needle though the inferior and superior borders of the keel in the midline. The small needle is then placed into the lumen of the large bore hollow needle and withdrawn back into the neck incision (**Figure 6**). The suture is secured over a segment of an intravenous cannula, with multiple suture. The keel is removed 7 to 14 days later, with the neck incision being partially reopened to remove the suture securing the keel (6).

An alternative approach is open reconstruction of the anterior commissure, without a keel. Once the laryngofissure is done, if the mucosa at the cut edge overlying the vocal cord is suitably mobile, pexing sutures are used to attach it to the cut edge of the thyroid cartilage, recreating an anterior commissure. 6.0 PDS suture is recommended, on double armed BV-1 needles, with these being placed through the mucosal edge, and then through the thyroid cartilage near the edge of the laryngofissure

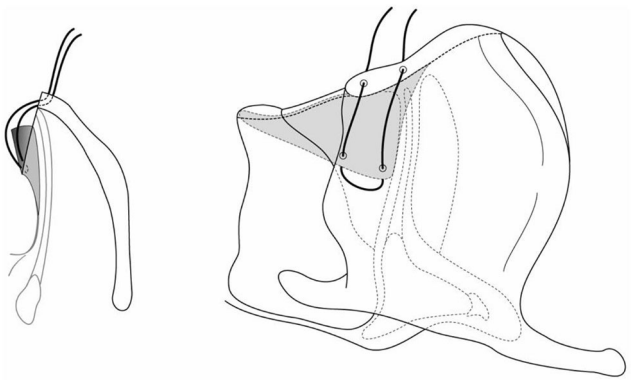

FIGURE 7 | The suture is placed as a mattress fashion.

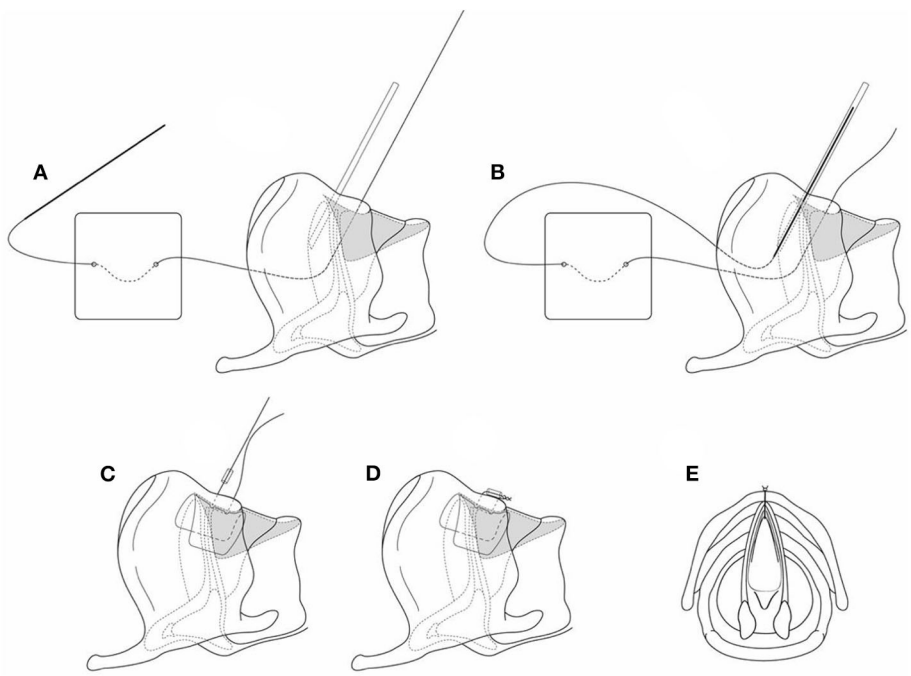

FIGURE 6 | (A–E) The silastic keel is inserted on the securing suture, and the suture is passed through a hollow angiocath to exit the larynx, and tied to secure the keel.

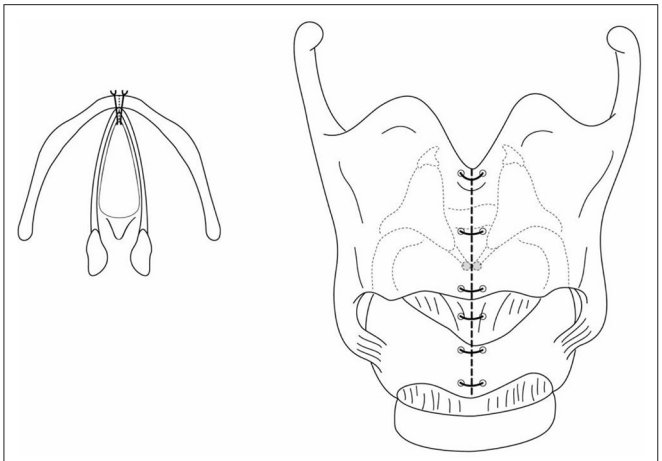

FIGURE 8 | After the pexing sutures are done separately each side, close the larygofissure.

at the level of the vocal ligament (**Figure 7**). This ligament lies at the junction of the lower third and upper two thirds of the laryngofissure in an infant. The suture is secured as a mattress fashion. A second pexing suture is placed below the initial suture to further mucosalize the raw incised edge of the web (**Figure 8**). The same procedure is then performed on the opposite vocal ligament. A segment of age-appropriate endotracheal tube is then placed into airway to determine whether an anterior cartilage graft will be needed for the subglottis. The airway is then closed, with intubation for 2 to 5 days (if this is a single stage procedure). This technique requires mobile vocal mucosa to achieve the mobility to "pex" the vocal cord mucosa back up to the thyroid cartilage, hence it is not suitable as a salvage procedure for a previously injured or operated web with scar formation. The mobile mucosa may provide a better long-term vocal outcome for its potential mucosal wave for vibration.

Options for cartilage grafts include thyroid alar and costal cartilage. Thyroid alar is useful for infants, and may be obtained from a superior lateral thyroid alar margin. Costal cartilage is an alternative choice and usually preferable for severe cases.

Total laryngeal atresia generally results in congenital high airway obstructive syndrome (CHAOS) unless there is a concomitant tracheoesophageal fistula. CHAOS is usually a pre-natal diagnosis on ultrasound and magnetic resonance imaging (11) with fetus presenting hydrops, everted diaphragms, mega-trachea, or prune belly syndrome. If recognized prenatally, ex-utero intrapartum treatment (EXIT) procedure to tracheostomy should be planned. As laryngeal atresia patients do not like to have a laryngeal lumen, and as the cricoid tends to be very small, repair is difficult. Repair is recommended after 4 years of age by cricotracheal resection with a complete laryngofissure. A prolonged postoperative stenting for at least more than 6 months is recommended. More than one procedure is typically necessary to achieve decannulation.

The selection of surgical management is usually surgeon dependent. Etiology of laryngeal web doesn't have impact on the choice of surgical procedure and the treatment outcome, whether it is congenital or iatrogenic (12). Surgeons make their decision based on their experience, and the judgement of the severity and complexity for the webs that they are facing. Some surgeons tend to start with endoscopic approach, and preserve open management as salvage procedures for failure cases. Advocators address the issue as open airway reconstruction is usually invasive and may have surgical and/or donor site morbidity. However, Alkan et al. reported higher re-adhesion/recurrence rate is correlated to higher Cohen Classification (12), for type 3/4 laryngeal webs lacking soft tissue for repair, direct open procedures may offer better surgical outcomes. Also, previous laser procedures tend to result in a complicated airway and have negative influence on following open surgical outcomes and more revisions (13).

For the past decades, both endoscopic and open procedures fail to provide promising results. The latest published case series, reported as high as 76 and 89% of recurrence rate for endoscopic and open approach, respectively (14). It once again emphasized the clinical and surgical challenging of laryngeal webs.

In summary, most congenital laryngeal webs are thick, thus open repair is warranted for an optimal outcome. It is recommended that all patients with congenital webs to be tested for 22q11.2 deletion syndrome. Scarred webs, whether congenital or acquired, are better managed with a keel placement, either open or endoscopic. Recreation of an anterior commissure with mobile mucosa of laryngeal webs by open reconstruction may provide a better voice quality even for severe congenital webs.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Pharyngomalacia in Neonates: The Missed Issue

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Background: Airway malacia (AM) is a weakness of the airway's frameworks making them collapsible during the respiratory phases. Although the larynx, trachea, and bronchus are the usual sites for malacia to occur, there is another important type of malacia that involves the pharynx. Pharyngomalacia (PM) or concentric pharyngeal wall inspiratory collapse (PWIC) is mostly missed during bronchoscopic evaluations in the neonates with noisy breathing because people are not aware of this condition.

Methods: This study aimed to evaluate the nasopharyngeal investigation among neonates suffering from noisy breathing. The retrospective study was undertaken to assess the frequency of PM and to propose indications for intervention in 100 neonates with noisy breathing. A thin fiberoptic bronchoscope was used to evaluate the upper airways under conscious status without any sedation in the neonates.

Results: A total of 100 neonates with noisy breathing from September 2015 to October 2018 were retrospectively analyzed. The most common presenting symptom was inspiratory stridor which was observed in 35 (92.1%) of cases. PM was diagnosed in 38 neonates (38%) including 27 (71%) males and 13 (29%) females. Seventeen (44.7%) cases had mild, 11 (28.9%) cases had moderate, and 10 (26.4%) cases had a severe type of PM. PM was more prominent at the velopharynx level in 15 (39.4%) cases, and it was accompanied by up to six synchronous airway abnormalities. The most frequent synchronous airway abnormality was laryngomalacia in 13 (34.3%).

Conclusion: PM is one of the causes of noisy breathing in infants. Since PM can be accompanied by the presence of other types of airway malacia, the issue becomes more complicated. On the other hand, lack of experience and facilities are two main causes for the accurate diagnosis and effective management among neonates. This study indicates that the investigation of pharynx is a missed part of the many workups that are used to diagnose the site of involvement in neonates with noisy breathing.

Keywords: neonates, stridor, pharyngomalacia, airway malacia, noisy breathing

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INTRODUCTION

The upper airway is defined anatomically as the airway segment between the nostrils and trachea at the level of the thoracic inlet, including five compartments: the nasopharynx (functional during nasopharyngeal breathing), oropharynx cavity (functional during oropharyngeal breathing), the hypopharynx, the larynx, and upper third part of the trachea within the level of the thoracic inlet. Due to the parallel anatomic arrangement between the oral and nasal cavities, they are

rarely the site of upper airway obstruction, except in cases of congenital malformation, massive head, and neck trauma and injuries from burns. Considering the pathophysiology of upper airway Obstruction (UAO), it is divided into dynamic (variable) and anatomical (fixed) obstruction. The major symptoms of UAO in neonates include noisy breathing and dyspnea. The severity of the symptoms directly depends on the severity of the obstruction. Noisy breathing in neonates is defined as unusual respiratory sounds during respiratory phases. The most important unusual sounds in neonates are stridor, wheezing, and snoring. Inspiratory stridor is the main symptom resulting from extra-thoracic airway partial obstruction. Differential diagnosis of stridor can be divided based on anatomical levels including supralaryngeal, laryngeal, and tracheal categories. Supralaryngeal causes of stridor consist of supralaryngeal causes which include vallecular cysts, thyroglossal cysts, and tongue dermoid or teratoma (1). Isolated pharyngomalacia is considered one of the causes in selected neonates with severe stridor (2). When the obstruction is acute and complete, such as bilateral choanal atresia, sudden dyspnea, or even suffocation may result at birth. But in chronic onset and uncompleted UAO, the neonate develops noisy breathing and dyspnea over time, especially during increased respiratory works such as feeding, crying, or sleeping in a prone position. The symptoms of dyspnea and noisy breathing are identical to those experienced with other types of airway malacia, such as tracheomalacia, bronchomalacia, or both. These similarities can lead to diagnostic confusion. Moreover, not all bronchoscopies looked at the pharynx for more investigation, and this makes pharyngomalacia a rarely diagnosed condition. This study was performed since the impact of PM as the major type of the UAO and its collaboration with other airway obstructions has not been well-understood yet.

MATERIALS AND METHODS

This retrospective study was done to investigate the role and the frequency of PM as a cause of noisy breathing in 100 neonates for 3 years. All records of neonates referred to our center with noisy breathing from September 2015 to October 2018 were included for reviewing. Bronchoscopy investigation is a routine investigation technique in neonates with noisy breathing that includes the following criteria: age <28 days, noisy breathing, dyspnea, cyanotic cough spells, aspiration and cyanotic spells during feeding, and recurrent apnea episodes. Aspiration is clinically defined as presenting choking, cyanosis, and apnea during feeding and is confirmed through fiberoptic endoscopic evaluation of swallowing (FEES) and barium swallow study (BSS). Exclusion criteria are as follows: age more than 1 month, parental disagreements, and no nasopharyngeal endoscopy examination.

The study was approved by the hospital ethical committee, and the parents or caregiver gave their informed consent to be enrolled in the study. Moreover, written informed consent was obtained from all the parents for both the publication and any accompanying images.

The assessment of upper airway dynamics was emphasized by using a thin (2.8 mm) flexible bronchoscope (Olympus Company, Japan) when the patients were on their spontaneous breathing with a nasal approach. Since different levels of sedation led to different dynamic and functional results and there was the possibility of interference of the results in the bronchoscopy evaluations, neither generalized anesthesia nor sedation was administered. For minimizing the possibility of airway irritation and spasm, lidocaine gel (2%) was applied all over the exterior surface of the FFB flexible bronchoscope. Based on the established protocol at the authors' department, a nasal cannula was inserted through one of the nostrils down to the nasopharynx to maintain oxygenation. No PEEP or positive ventilation was used at the time of endoscopy evaluations as it could interfere with the flaccidity of airway walls and the final reports. According to the bronchoscopy investigation, PM was defined in multiple sites as follows: from the level of the hard palate to the tip of the uvula (velopharynx), from the end of the uvula to the tip of the epiglottis (oropharynx), and finally from the tip of the epiglottis to the vocal cords (hypopharynx). As to the best of the author's knowledge, there were not any grading scales regarding the severity of obstruction in PM. Thus, the author used a new modified grading scale based on the one that has been used for adenoid hyperplasia and tracheomalacia depending on the present airway obstruction and severity of the symptoms. So, it has been graded as mild, moderate, and severe when an obstruction was <50%, between 50 and 75%, and more than 75% of the airway diameter, respectively.

To prove the exact role of PM in induced symptoms, positive pressure ventilation of 5 cm water was applied by closing the anesthesia bag valve and bypassing the obstruction level through using the nasopharyngeal tube. These maneuvers aborted the pharyngeal wall collapse and the symptoms. Patients affected by mild to severe PM benefited from supportive medical management while airway structural stability was expected with increasing age. The supportive care used included nasal washing with normal saline, nasopharyngeal mucosal gentle suctioning, antireflux positions, and therapy with oral proton-pump inhibitors (PPIs) like omeprazole, nasopharyngeal catheters, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP).

All patients underwent a follow-up program adjusted to individual patients' conditions and needs in terms of the different types of PM every 2–3 months for up to 3 years.

RESULTS

In a retrospective review of consecutive endoscopic evaluations and clinical data of 100 (48 female and 52 male) neonates with UAO, PM was diagnosed in 38 neonates (38%) including 25(65.8%) males and 13 (34.2%) females. The age of neonates at the time of endoscopy diagnosis was from 7 to 28 days after birth. With regard to the extent of PM, the number (present) of children with mild, moderate (**Figure 1**), and severe (**Figure 2**) were 17 (44.7%), 11 (28.9%), and 10 (26.4%), respectively. Based on the results of the bronchoscopy investigations, PM was most

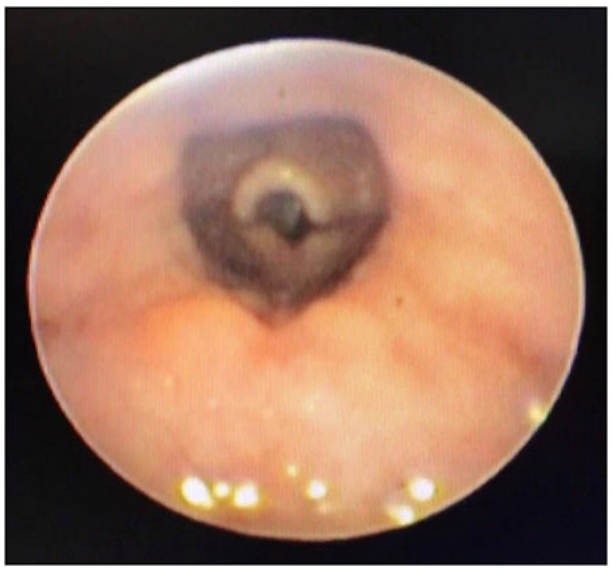

FIGURE 1 | Moderate PM.

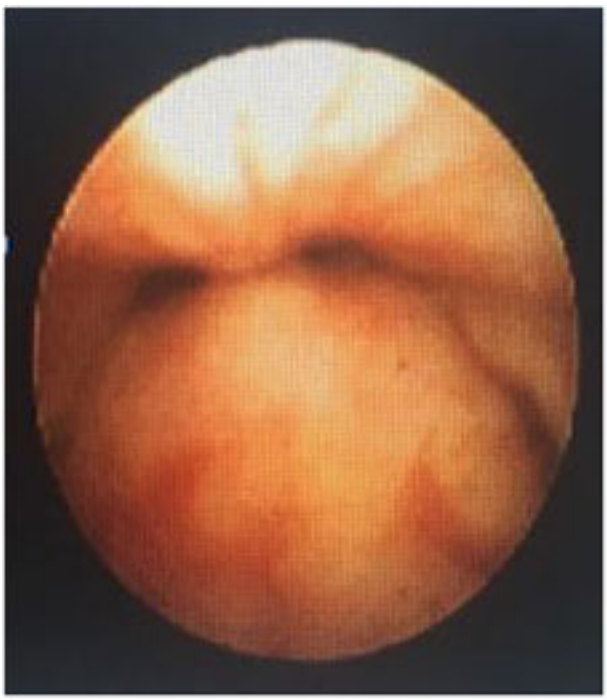

FIGURE 2 | Severe PM.

prominent at the velopharynx level 15 (39.4%) followed by hypopharynx 13 (34.2%), the whole length of pharynx 7 (18.4%), and oropharynx 3 (8%). The most common presenting symptoms were inspiratory stridor 35 (92.1%), cyanotic cough spell 27 (71%), aspiration and cyanotic spells during feeding 21 (55.2%), and recurrent apnea 18 (47.3%).

This study also showed that PM was accompanied by up to six synchronous airway abnormalities; the most frequent ones were laryngomalacia 13 (34.3%), tracheomalacia 12 (31.5%), bronchomalacia 6 (15.8%), larygotracheobronchomalacia 3 (8%), tracheoesophageal fistula (TEF) 2 (5.2%), and posterior laryngeal cleft 2 (5.2%). The results are presented in **Table 1**. Generalized hypotonia was the most common associated systemic finding 4 (12%). There were two neonates with Down syndrome and one with VACTER syndrome suffering from severe PM at the level of velopharynx.

Non-invasive positive ventilation devices including CPAP and BiPAP were used in 21 (55.3%) neonates with moderate to severe PM. The duration of use of these devices varied depending on the age and severity of the PM (mean, 7 ± 3.5 months). Four (10.5%) cases including one patient with VACTER, one with Down syndrome, one with posterior laryngeal cleft, and one with TEF underwent tracheostomy.

In the follow-up, 35 (92%) of the cases became asymptomatic from 10 to 24 months (mean, 18 ± 5 months) by using supportive care.

DISCUSSION

Noisy breathing is one of the most common indications for doing bronchoscopic investigations in neonates. UAO and LAO are the main causes of these abnormal breathing sounds. UAO is a potentially severe and life-threatening complication among neonates. Tracheomalacia is the most common congenital UAO among this age group (1). Its incidence seems to be underestimated but reported as about 1 in every 2,100 children (3). Most children are either asymptomatic or minimally symptomatic, and most cases involve posterior malacia of the trachea, with associated broad tracheal rings. On the other hand, PM is a dynamic obstruction of the air column proximal to the glottis during inspiration. The author's objective was to assess PM's incidence and its contribution to the symptoms of UAO and to propose indications for intervention.

As 38% of neonates had various types of pharyngomalacia, this study showed that there are some important misdiagnoses in previous studies regarding the causes of noisy breathing in neonates. A wide variety of PM exists that is often missed first, as the oral approach is the often-used routine bronchoscopy route for any investigations done by a pulmonologist. Secondly, most pediatric bronchoscopists may not be familiar with the anatomical and physiological aspects of the upper airways especially in the neonates and young infants. Thirdly, it is difficult to do the bronchoscopy setup in small neonates especially in the unstable ones, and lastly, neonatal bronchoscopy facilities are unavailable in many centers. Based on this study, male neonates were more prone to have PM than females. There is a scant research regarding the related issue in the literature. However, based on bronchoscopic investigations, this may be because male neonates have longer velopharynx compared with female neonates (4). Previously, laryngomalacia (87.2%), pharyngomalacia (33.3%), and tracheomalacia (10.3%) were

TABLE 1 | Detailed data.

Demographics	***n* = 38**
Sex (male)	25 (65.8%)*
Sex (female)	13 (34.2%)*
Birth gestational age (weeks)	36 (25-41)$^{+}$
Age at the time of bronchoscopy (days)	16 (7-28)$^{+}$
Severity	
Mild	17 (44.7%)*
Moderate	11 (28.9%)*
Severe	10 (26.4%)*
Site of maximum involvement	
Velopharynx	15 (39.4%)*
Hypopharynx	13 (34.2%)*
Whole length of pharynx	7 (18.4%)*
Oropharynx	3 (8%)*
Symptoms	
Stridor	35 (92.1%)*
Cyanotic cough spell	27 (71%)*
Aspiration (cyanotic spells during feeding)	21 (55.2%)*
Recurrent apnea	18 (47.3%)*
Synchronous airway abnormalities	
Laryngomalacia	13 (34.3%)*
Tracheomalacia	12 (31.5%)*
Bronchomalacia	6 (15.8%)*
Larygotracheobronchomalacia	3 (8%)*
Tracheoesophageal fistula (TEF)	2 (5.2%)*
Posterior laryngeal cleft	2 (5.2%)*

**Frequency (percentage). $^{+}$Median (min-max).*

reported as the three most prevalent findings on endoscopy of neonates with sleep apnea (5). PM was also reported as an under-recognized rare condition in patients with Down syndrome who had sleep apnea (6). Thus, PM may account for one of the major causes of obstructive sleep apnea. In the study by Shatz et al., the majority of children had obstruction related to pharyngeal hypotonia and collapse. They also mentioned that PM can lead to prolonged hospitalization and intensive care admission and may raise the difficulty in management issues (7). The severity of PM was measured through severe retractions and respiratory compromises like respiratory failure, apnea, cyanotic spells, the need for more respiratory supports depending on additional oxygen, extubation failure, choking spells while feeding, and poor weight gain. Moreover, as there were no standard severity grading scales especially in neonates, the author considers the percentage of stenosis as the described severity scales from mild to severe. According to this scaling, most of the cases had mild to moderate PM.

Similar to other types of airway malacia, PM seems to be a self-limiting condition and spontaneous recovery occurred within 36 months. Although mild PM is watched expectantly and anticipated to improve with time, there were more severe symptomatic PMs.When it occurs with other airway insults, it warrants interventions like non-invasive ventilatory supports (nasopharyngeal catheters, CPAP, bilevel instruments) and rarely may need surgery in some cases (8, 9).

In this study, most of the index cases (92%) became asymptomatic due to supportive care including antireflux position and therapy, the decrease of mucosal stickiness of the nasopharyngeal wall with nasal spray 10–15 min before feeding and 3–5 ml normal saline oral solution after feeding, gentle nasal suctioning, and small frequent feeding.

In neonates with compromised airway disorders where swallowing interrupts with normal smooth breathing, this causes sucking-swallowing discoordination (SSD) leading to aspiration although the exact incidence is not well-established (10, 11).

In this study, more than half of the patients had aspiration due to SSD clinically presented with cyanotic spells during feeding and was approved by FEES and BSS. Direct vision investigation with FEES study revealed that aspiration became effectively diminished by resolving the PM-induced partial obstruction using nasopharyngeal bypassing, gentle mucosal suctioning, and patient positioning with 30–45% of body (not neck flection) elevation.

Progressive and severe PM cases required a nasopharyngeal catheter for bypassing the stenotic level; CPAP or BiPAP form weeks to months. Four cases underwent tracheostomy procedures especially those with concomitant syndromes (VACTERL and Down syndromes). It seems the rest of the cases became asymptomatic as they were followed up until the time of publishing the data.

This study has some limitations including the nature of retrospective studies, lack of previous research studies on the topic, limited access to data, and a combination of abnormalities which on their own can cause noisy breathing.

The incidence of PM among neonates with UAO was beyond expectations in this study, and its role in UAO deserves greater recognition. This study also showed a combination of abnormalities, which on their own can cause noisy breathing. Its commonly associated abnormalities can include laryngeal clefts, TEF, and bronchomalacia. The current gold standard for the diagnosis of PM is a dynamic evaluation under direct vision through nasopharyngoscopy. A better diagnosis of PM will improve the treatment of UAO.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MM wrote the manuscript and approved it for publication.

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REVIEW
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Surgical Options for Pediatric Bilateral Vocal Cord Palsy: State of the Art

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Management of pediatric bilateral vocal cord palsy (BVCP) is a controversial and challenging topic. It may represent a severe obstructive condition usually associated with respiratory distress, and, in such condition, tracheostomy has been considered the gold standard for a long time. Many surgical options have been described and used to increase the glottic space in BVCP (1), with ongoing research of less invasive techniques. The challenge and current trend in our department and in many major pediatric centers is to avoid tracheotomy through an early treatment. Many techniques introduced in the last decade reduced the number of tracheotomies and increased the decannulation rate. Furthermore, we observed a recent increase in attention to preserve the quality of the voice with new techniques, such as endoscopic arytenoid abduction lateropexy which is in our opinion an important innovation to improve glottic space with satisfactory voice results. We present a review of the literature about the evolution of the treatment options for pediatric BVCP during the years.

Keywords: bilateral vocal cord palsy, pediatric, surgical options, voice quality, airway surgery

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INTRODUCTION

Vocal cord paralysis (VCP) is the second most common congenital laryngeal anomaly in pediatric age (10–15%) (2).

Unilateral VCP and bilateral VCP differ in clinical presentation, etiology, and treatment. Bilateral vocal cord paralysis (BVCP) can be characterized by stridor, respiratory distress, suprasternal, and chest retractions, sleep apneas, and failure to thrive, and it represents up to 62% of all pediatric VCPs (3). Instead mild stridor, aspiration, and hoarse and breathy voice are generally suggestive of unilateral vocal cord paralysis (UVCP).

VCP results from laryngeal innervation disorders, posterior glottic stenosis, or cricoarytenoid joint's (CAj's) fixation. All the motility anomalies of the larynx are described with the term "laryngeal immobility."

An awake laryngeal endoscopy is the essential test for diagnosis of the paralysis, and a complete airway endoscopy under general anesthesia is always recommended to exclude other airway-associated pathologies and to differentiate the paralysis from vocal cord fixation (cricoarytenoid joint ankylosis, posterior glottic stenosis). About 45% of the cases of congenital BVCP have other airway diseases, and the most common are laryngomalacia, subglottic stenosis, and tracheomalacia (4).

In infants and children, VCP has mainly neurological, traumatic (birth trauma), and iatrogenic (post-surgical complications) (4–8) etiology. An MRI is often required to evaluate the central

nervous system. In about one-third of the neurological cases, Arnold–Chiari II malformation is present with concomitant hydrocephalus and myelomeningocele. Furthermore, a large number of BVCPs are idiopathic (4, 5) and according to the literature, spontaneous recovery of vocal cord motility is possible within 1 or 2 years over the two-thirds of patients (3, 9, 10).

The treatment's choice has many variables; in particular, urgent intubation may be required in case of severe respiratory distress to ensure a safe airway. Placement of a tracheostomy can be required (11) in order to wait for a spontaneous recovery or the therapeutic choice.

In the last decade, the possibility of an early treatment avoiding tracheotomy has been considered, in particular with the proposal of minimally invasive treatments with preservation of the vocal folds, such as endoscopic arytenoid abduction lateropexy (1) or anterior–posterior cricoid split (12).

The best timing of surgical intervention is not standardized, and it is generally discussed case-by-case. Investigating the etiology of paralysis is crucial to predicting the possibilities of recovery and the timing of treatment. Other important prognostic variables are presence of comorbidities, associated airway diseases, age of the patients, and severity of the clinical condition.

Several surgical procedures to improve the glottic respiratory space have been proposed over the years, both endoscopic and open surgery, but a standard treatment has not been established.

The aim of this paper is a review of the literature on the treatment's options on pediatric bilateral vocal cord paralysis, focusing on the most recent techniques and the most promising and conservative approach currently available in this delicate field.

SURGICAL OPTIONS

Many surgical options have been described and used to increase the glottic space in BVCP (13), with continuous research of less invasive techniques. In 1946, Woodman (14) published a series of patients treated by arytenoidectomy and suture lateralization of the vocal process performed with the external posterolateral approach. This technique was reported with good results also by Cohen in 1973 (15) and Narcy in 1990 (16).

Other authors described partial and total arytenoidectomy with lateralization of the vocal process through the laryngofissure approach, making a midline incision of the thyroid cartilage (3, 17).

Thornell was one of the firsts to promote endoscopic procedures; he performed endoscopic arytenoidectomy using electrocautery (18). The development of the CO_2 laser gave new possibilities, ensuring greater precision, so in 1984 Ossoff et al. (19) described endoscopic CO_2 laser posterior cordotomy and in 1989 Dennis and Kashim (20) endoscopic laser CO2 arytenoidectomy (**Figure 1**).

In 1993, Crumley (21) proposed a variation of this procedure: endoscopic laser medial arytenoidectomy, preserving part of the cartilage including the vocal process, to reduce the consequences on the voice function. Bad voice quality is the main adverse effect of the surgery for BVCP, in particular after aritenoidectomy and posterior cordotomy (22, 23).

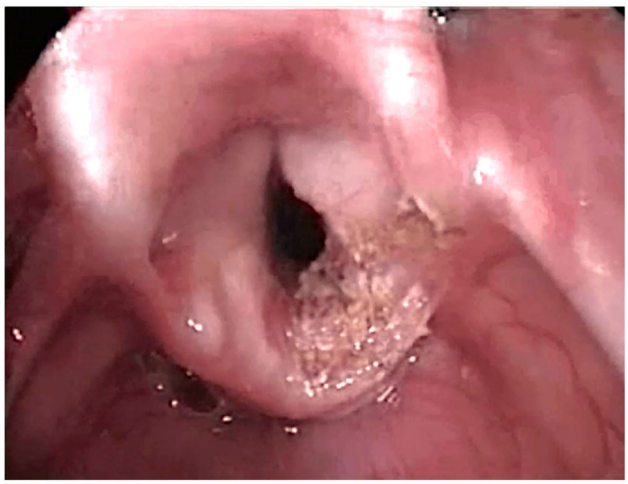

FIGURE 1 | CO_2 Laser right partial arytenoidectomy.

Most of the literature about the treatment of BVCP is referred to adult patients. One of the few describing a series of pediatric patients compared results of endoscopic vs. open arytenoidectomy [1994, Bower et al. (24)]. The series of 30 patients underwent endoscopic or external arytenoidectomy and lateralization, resulting in a higher decannulation rate for open arytenoidectomy (84%) than the endoscopic arytenoidectomy one (56%).

In 1989, Dennis and Kashima (20) introduced laser partial cordotomy (**Figure 2**) as a new endoscopic technique, which consisted of a triangular excision of the posterior true vocal fold and false vocal fold to improve the glottic respiratory space. In 2001, Friedman et al. (25) reported a series of pediatric patients all decannulated after posterior cordotomy. A combined endoscopic use of the two methods may be indicated (26).

A surgical revision may be often necessary both post arytenoidectomy than post posterior cordotomy for the presence of scar tissue or granulations, but the decannulation rate is high (27–29).

The use of new technologies has recently increased, with functional improvement and lower risk of thermal damage to the surrounding tissues: in 2015, Googe et al. (30) presented 14 cases of arytenoidectomy by coblator, and in 2018 Basterra et al. (31) described posterior cordotomy in bilateral vocal cord paralysis using monopolar microelectrodes and radiofrequency in 18 patients.

Ozturk et al. (32) compared laser cordotomy and diathermy-assisted cordotomy. Both the techniques gave a sufficient increase in respiratory space, stable over time, confirmed by respiratory functional test results. However, they showed a deterioration in terms of voice quality without significant differences between the two procedures.

Another procedure to improve the laryngeal respiratory space is the posterior cricoid split with rib grafting. This surgery,

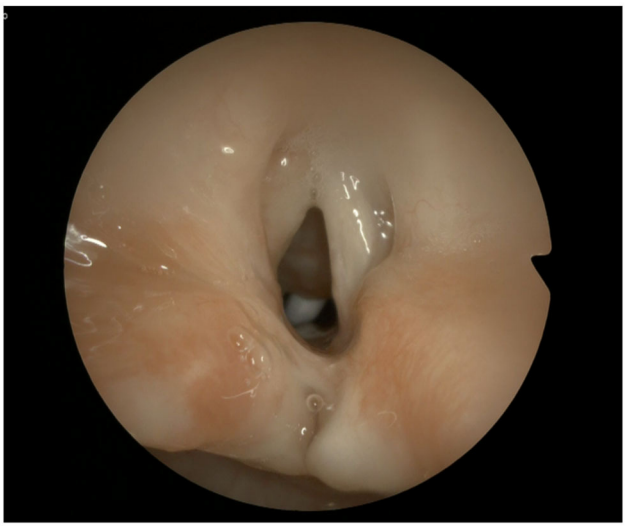

FIGURE 2 | Result after CO_2 laser left posterior cordotomy.

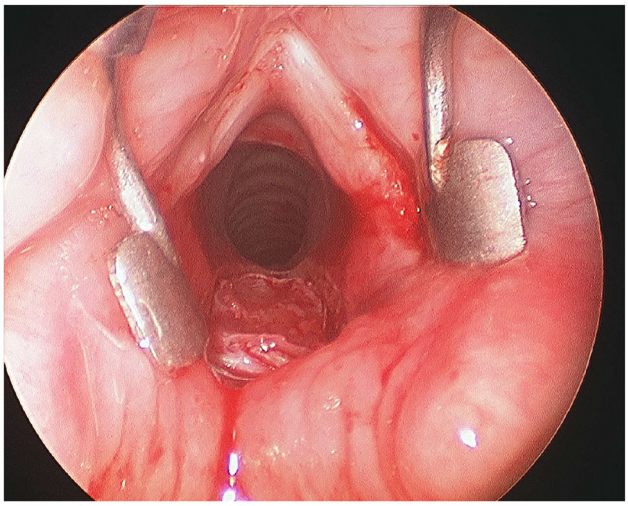

FIGURE 3 | Endoscopic posterior cricoid split with rib grafting.

mainly indicated for the treatment of glottic–subglottic stenosis and posterior glottic stenosis (33, 34), consists of a posterior enlargement of the interarytenoid space by splitting the cricoid plate and placing a rib cartilage graft, through laryngofissure (35) or using an endoscopic approach (12) (**Figure 3**). In 1994, Gray et al. (35) described the treatment of three cases of BVFP using this surgical procedure, with good outcomes in terms of decannulation (each patient was decannulated), and in 2003, Inglis et al. (12) published the results obtained in a series of 10 patients who underwent this surgery through endoscopic technique. For the latter, an excellent laryngeal and subglottic space exposure is crucial to performing midline posterior cricoid incision by CO_2 laser and splitting and where to put the cartilage rib graft opportunely shaped without appose sutures [no cases of graft dislodgment were described by Inglis in his paper (12)]. Recently, on 2017 again Inglis et al. (36) published a review of their experience about endoscopic posterior cricoid split during the last fifteen years. They described a series of 33 patients (32 had tracheostomy) with different pathologies (subglottic stenosis, posterior glottic stenosis, and bilateral vocal cord immobility) and a rate of decannulation after this surgery of 65.6% (only 28.6% for bilateral vocal fold immobility). This endoscopic procedure has the advantage of preserving the anatomy of the vocal folds and, theoretically, does not cause problems in case of spontaneous recovery of the motility and does not preclude the possibility of other surgeries, but its success was different for the pathologies treated, with worse results in subglottic stenosis combined with vocal cord paralysis. Furthermore, this surgery can be complicated by dysphagia and tracheotomy was considered before or during the endoscopic posterior cricoid split to prevent the risk of respiratory complications in case of dislodgment of the graft (36).

In 2018, Rutter et al. (37) proposed their results with the use of anterior–posterior cricoid split in a series of children in order to avoid tracheotomy. It consists in opening both sides of the cricoid cartilage endoscopically and dilating with an overestimate ETT for about a week. Between 2010 and 2016, they treated 19 patients with this technique and 14 (74%) avoided tracheostomy, demonstrating the effectiveness of the treatment under correct circumstances and so the opportunity to continue with further studies.

In 1922, Rethi (38) described the possibility of glottic enlargement with a lateralization of the vocal cord performed through a laryngofissure. Over the years, this technique has been resumed and perfected with the endoscopic approach as reported by Kirchner et al. in 1979 (39) and Ejnell et al. (40, 41). The laterofixation of the vocal cord is performed, after removal of the thyro-arytenoid muscle, by placing two sutures at the posterior third of the glottis, for each passing the thread above and below the vocal fold and pushing it out through the larynx, up to the skin where they are fixed in a little subcutaneous pouch over the muscle level.

Lichtenberger described the endoscopic vocal cord lateralization (42, 43) performed by using the Lichtenberger needle carrier (44), which more easily allows to pass the thread below and above the vocal fold through the thyroid cartilage, from the endolaryngeal lumen up to the skin. This procedure has been considered reversible from the authors; in case of recovery of vocal cord motility, the suture can be removed and a success rate up to 98% is described in literature (42, 43). Several variations of this technique have been proposed. Mathur et al. (45) tried to simplify the procedure using different instruments to reduce manipulation of the needle and thread inside the larynx and so the risks during the surgery. They performed lateralization of the vocal fold in a series of 10 pediatric patients by a set of spinal needles and a 2–0 stitch-passed extra laryngeal under endoscopic guidance, with a decannulation rate of 100% in the ten patients (45).

Woodson et al. (46, 47) described a very interesting alternative to laterofixation: arytenoid abduction. This technique simulates the natural contraction of posterior cricoarytenoid muscle and abduction of the vocal fold (**Figures 4A,B**). With a transverse skin incision at the midlevel of the thyroid cartilage, the posterior border of the thyroid cartilage is exposed to perform a suture laterofixation of the arytenoid cartilage by a permanent suture placed through the vocal process of the arytenoid and tied.

In 2010, Rovò et al. (48) proposed a new instrument for endoscopic arytenoid lateropexy, a modified endolaryngeal thread guide instrument (ETGI) based on a movable curved blade that guides the thread in and out from the endolaryngeal space up to the skin, with the aim to easily form a loop around the vocal process of the arytenoid cartilage and getting its abduction. They reported the results of the treatment of vocal cord immobility, including 22 adult patients with BVCP, showing how endoscopic arytenoid lateropexy is an effective solution for it (48).

In 2017, Madani et al. (1) described the possibility of using endoscopic arytenoid abduction lateropexy in 4 newborns by a new miniaturized ETGI, with good respiratory outcomes, no dyspnea, or swallowing disorder and satisfactory results about voice quality. Recently, the same Hungarian group (49) evaluated long-term results on the same patients after 3 years from endoscopic arytenoid abduction lateropexy. In terms of breathing, voice, and swallowing, every patient had durable resolution of dyspnea, a normal per os diet, an appropriate growth and development, and a normal voice in 2 cases and slightly impaired voice in 1 case.

Szakács et al. (50) published a comparison of the effects of different endoscopic glottis-widening procedures on cadaver; endoscopic arytenoid abduction lateropexy was the most effective and least destructive on phonation structures, providing with a physiological adduction movement the best phonation closure especially if recovery of adductor function occurs. Furthermore, the authors describe the reversibility of this technique without permanent damage to the vocal folds (49).

None of the surgical techniques above described can restore the normal laryngeal physiological movement of adduction and abduction.

With this purpose, laryngeal reinnervation techniques have been proposed.

In 1974, Miehlike (51) studied on animal model the anastomosis of the distal posterior branch of the laryngeal nerve (innervating the posterior crico-arytenoid muscle) with the main funiculus of the recurrent laryngeal nerve dissected out of the vagus. In 1975, Tucker (52) described a reinnervation procedure in adults consisting in dissecting a branch of the ansa hypoglossi joined to the corresponding area of omohyoid muscle to suture it at the level of the posterior cricoarytenoid muscle. In his series, three of five patients were decannulated with the increased glottic airway in over 80% of patients, but his results have never been reproducible in subsequent studies.

More recently, the use of foreign nerves has been deepened for the laryngeal reinnervation surgery in the treatment of bilateral paralysis. As described by Marina et al. (53) in 2011 and Li et al. (54) in 2013, the phrenic nerve can be used with good results to obtain a branch as a nerve substitute because it has a homogeneous composition of motoneurons involved during inspiration, with improvement of the movements in BVCP up to 93% (54).

Usually in BVFP, obstructive respiratory symptoms are predominant suggesting that adducting movement is partially preserved, so restoring the abduction function is the main purpose of these techniques with the possibility also of transecting the anterior laryngeal nerve branch to reduce the activity of the adductor muscles (53).

Recently, the rerouting of the thyrohyoid nerve for laryngeal reinnervation has been considered (55, 56) to reduce the length of the nerve graft and to find a reasonable alternative when ansa cervicalis is not available as a donor nerve, with good functional results and vocal outcomes (lower GIRBAS scores, higher maximal phonation time, stable, or improved postoperatively voice quality) (56).

Laryngeal reinnervation is a promising technique for BVCP, but the studies are still limited to adults with very limited experience in children (57) and in many cases, they refer to the treatment of unilateral vocal cord paralysis.

Alternative therapies have been investigated in recent years too, such as stem cell implant and gene therapy. Stem cell therapy for tissue regeneration in vocal cord paralysis may be applied by the use of autologous muscle-derived stem cells as Halum et al. (58) proposed in 2007 obtaining in rats the attenuation of muscle atrophy.

In 2016, Dirja et al. (59) tried the use of induced pluripotent stem cells with evidence of good differentiation in muscle cells *in vitro* and 2 weeks of survival in thyroarytenoid muscle of rats. Further papers show that adipose-derived stem cells (60) and olfactory ectomesenchymal stem cells (61) represent an interesting choice for this therapy; in particular, the latter have a high neuroregenerative potential in animal models. Always with the aim of promoting laryngeal nerve regeneration and muscle trophism, the idea of gene therapy has been proposed in several studies. It provides to use genes that encode neurotrophic factors for neuronal regeneration and growth factors for muscle cell proliferation and differentiation (62). These genes are linked to vectors that are injected into the laryngeal nerve and muscles (63, 64).

In 1998, Shiotani et al. studied the effect of insulin-like growth factor I gene in rats' denervated larynges (65), reporting an improvement of the size of muscle fibers and the number of axon terminals in the thyroarytenoid muscle, and in 2007 the effect of an adenoviral vector-encoding glial cell line-derived neurotrophic factor (GDNF) on the nucleus ambiguus of rats with vagus nerve injury (66), showing a lower loss of motoneurons after this treatment.

Both gene therapy and stem cell therapy are still experimental with *in vitro* and animal studies, therefore requiring further research and finding the solution to some problems such as ineffectiveness in preventing synkinesis, the risk of damage by viral vectors, and poor cell culture survival (51, 67).

Currently, functional electrical stimulation is another approach in progress for BVCP treatment. In 2016, Mueller et al. (68, 69) described the results of laryngeal pacing implant in 9 patients with evidence of spirometric parameter improvement,

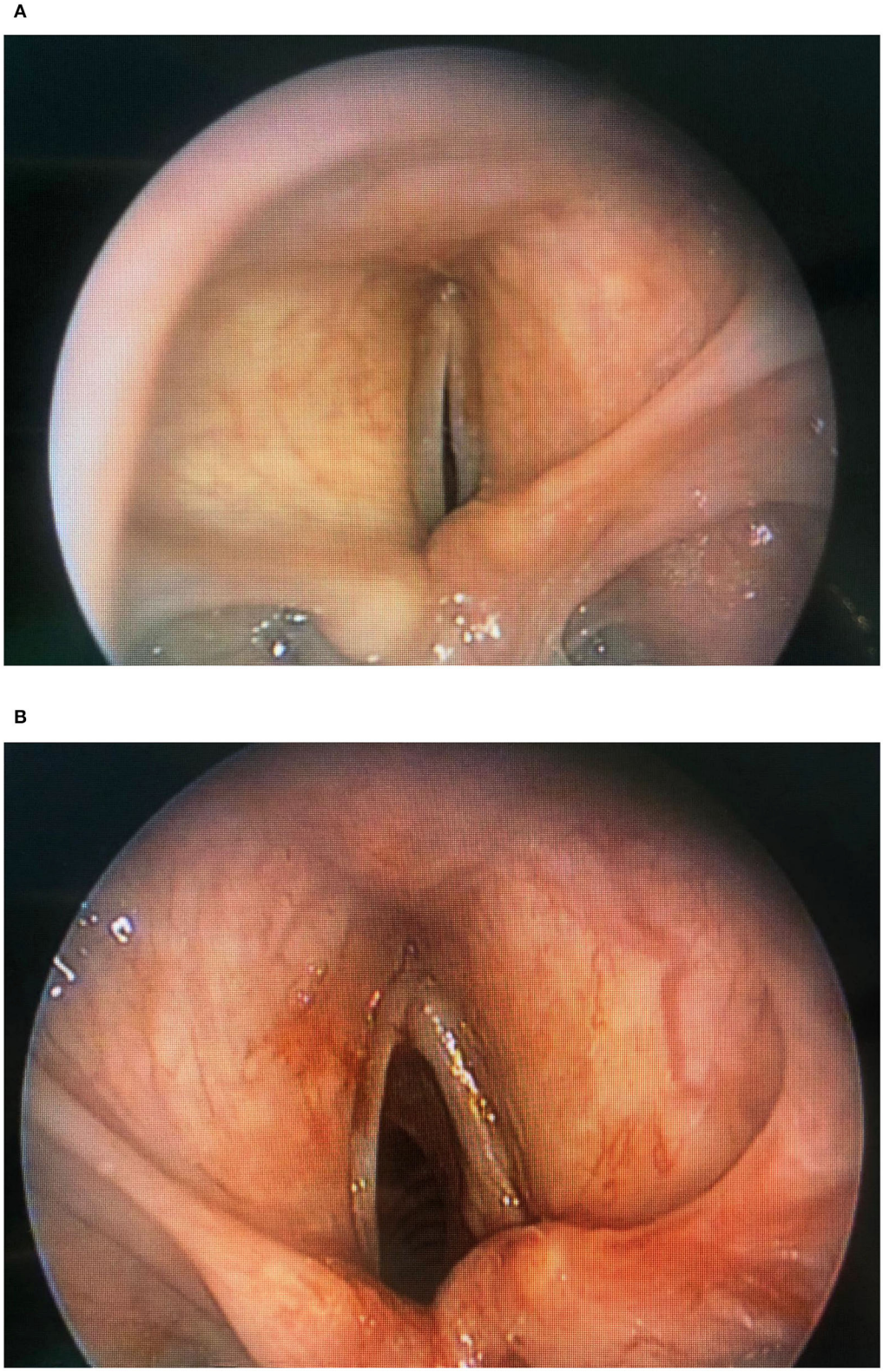

FIGURE 4 | (A) Endoscopic arytenoid lateropexy (before surgery). **(B)** Endoscopic arytenoid lateropexy (after surgery).

in particular of peak expiratory flow, without negative effects on the voice quality and swallowing. The first who introduced the functional electrical stimulation were Zealear and Dedo in 1977 (70), acting on unilaterally paralyzed cricothyroid muscle of the canine. In the following years, other authors reported the results about the stimulation of paralyzed posterior cricoarytenoid muscles, always in the canine model (71–73). Then in 1996, Zealear et al. (74) described the possibility of laryngeal pacing in humans, presenting in 2003 the results of unilateral laryngeal pacing in 7 patients with BVCP using an external device (75). In 2019, Muller and Pototschnig (76) showed their technique of electrical stimulation of the recurrent laryngeal nerve: one of the pacer electrodes is inserted into the PCA muscle, and the pacer is placed in a subcutaneous pocket over the sternum with another electrode on the lateral chest. Furthermore, they underline the importance of selection of patients who could have benefits from this procedure, as, for example, the presence of aberrant or synkinesis reinnervation is essential to ensuring good clinical performance of laryngeal pacemakers, although it is commonly considered an unfavorable condition for recovery of vocal cord movement (76). This technique has a high potentiality, ensuring a ventilatory improvement without compromising voice and swallowing (67). It could overcome the other surgical approach (76), and it has been described as superior to posterior cordotomy in ventilation and voice outcomes by Li et al. (77). However, it is still a complicated experimental procedure, more expensive than other surgeries considering also that the device must be replaced at least every 10 years (66), and so far there is no pediatric experience.

The comparisons of the different techniques do not show significant differences in literature, as reported by Gupta et al. (78), who found similar results in the decannulation rate between laser cordectomy, arytenoidectomy with fold lateralization, and endoscopic fold lateralization in a series of 61 patients (adults and children).

Partial arytenoidectomy and posterior cordotomy give an immediate respiratory space enlargement as well as vocal cord laterofixation, but the latter is certainly more conservative for laryngeal anatomy.

Laterofixation can be considered for its minimal invasiveness and reversibility (67, 79), ensuring minor impairment of voice. In particular, endoscopic arytenoid abduction lateropexy, characterized by an arytenoid abducted movement that preserves the vocal cordal anatomy and therefore the integrity of the mucosal wave, is a valid approach to obtain good respiratory outcomes preserving a good voice quality. During the last 2 years, at our Airway Surgery Unit, we focused the attention on this technique with excellent results that we are analyzing for an upcoming publication, characterized by significant improvement of the respiratory space and high decannulation rate maintaining a good quality of voice.

After diagnosis of BVCP, time of observation may be indicated especially in patients in whom spontaneous recovery can be expected (79), but the challenge and current trend in our department and in many major pediatric center is to avoid tracheotomy through an early treatment (67, 79). Our opinion, supported by literature (48), is that the endoscopic arytenoid abduction lateropexy is a good approach for an early treatment also in infants considering its characteristics of preservation of the vocal cord anatomy and reversibility in case of spontaneous recovery.

Exactly to evaluate the possibility of spontaneous recovery, laryngeal electromyography could have an important prognostic role identifying the candidates for early intervention, as described in several studies (80–84). Laryngeal electromyography shows the motor unit potentials, through hooked wire electrodes inserted into the thyro-arytenoid muscle and the posterior cricoarytenoid muscle, and it can be used to differentiate between mechanical (i.e., cricoarytenoid joint fixation) and neurological impairment of vocal fold and to localize the neuromuscular lesion.

As reported in a recent paper by Giotakis and Pototschnig (85), the presence of volitional activity in the multiple LEMG findings indicates the possibility of a full late recovery of laryngeal motility, allowing to select the cases for a wait-and-see strategy or a reversible approach, rather than a permanent laryngeal surgery. However, in the literature the opinion about the predictive value of this test is under debate, with data ranging from 13 to 96% (80, 81, 86).

SUMMARY

Identifying the best surgical approach for BVCP in pediatric patients is not easy, considering also that the experiences reported by many authors concern adult patients with very few and small series in children and that the comparisons of the different techniques do not show significant differences in literature.

Most studies report the results in terms of respiratory improvement and decannulation rate, with less attention to voice quality evaluation or assessing swallowing, even if common side effects of the BVCP surgery are dysphonia, dysphagia, and aspiration, but comparing with previous reviews in pediatrics' BVCP treatments, in addition to the global trend to reduce invasiveness, we observed a recent increasing in attention to preserve the quality of the voice.

The new techniques and therapies described above still require further studies and trials but are promising for the future in order to overcome more destructive surgical techniques and giving a potential dynamic functional recovery of the larynx.

AUTHOR CONTRIBUTIONS

MT, DM, AS, MLT, and SB contributed conception and design of the study. MT, DM, and AS wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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OPINION
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Teamwork in Airway Surgery

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INTRODUCTION

The twentieth century saw the gradual disappearance of the heroic individual doctor and the emergence of specialities with distinct governance structures through colleges and societies. These defined training and issued qualifications. In our world, cardiothoracic surgery split from general surgery, pediatric surgery from general surgery and ear, nose and throat surgery emerged in parallel. The separation produced rapid advances in each field but, as an unexpected consequence, the disciplines grew apart, developing their own ways of working and their own tribal cultures. Our patients (and their conditions) did not recognize this, and they would find that the way in which their disease was treated varied widely–defined largely by the speciality with which they first came into contact.

The management of complex airway disease in children exemplifies these problems, but also offers a solution. In the late twentieth century, patients were referred to individual surgeons who applied the skills of their own discipline to varying, but imperfect effect. Inter-discipline referral was rare, and sometimes difficult because the geographic location of services had become separated to different hospital sites in previous years. Sadly, and as we all now know, affected children often had problems which crossed the constrained boundaries which we physicians had drawn up. Tracheal stenosis is often combined with cardiovascular anomalies and genetic abnormalities are frequent. Upper gastro-intestinal tract issues including swallowing problems abound. Patients attending one speciality were referred to another for consultation on a *transactional* basis. Indeed, in dominantly private healthcare systems, this remains the case, as it can increase incomes to all parties. This slows decision making, fails to integrate views effectively and weights decision making in favor of the physician to whom primary referral is made. Our primary aim as physicians is "first, do no harm." As Hull and Sevdalis pithily stated (1) "Teams create safety," and as we hope to outline in this paper, teamwork also improve outcomes, creates efficiency, reduces cost and promotes research. Achieving these goals is good for patients and for the wider healthcare system.

SOME LOCAL HISTORY

In the United Kingdom in the 1980s and 90s, referrals for small children with long segment congenital airway stenosis (LSCTS) passed through a series of gateways to pediatric or cardiac intensive care units, largely because of the resuscitative skills held by the staff there. Surgery tended to default to cardiac surgical teams because of the high incidence of associated cardiovascular anomalies and the need for cardiopulmonary bypass for repair. The incidence is low, and so each center saw a tiny number of patients, and experience was hard to acquire. There were only a few short case series in the literature upon which to base treatment choices, and few contained sufficient detail to be confident about all the relevant technical details and none had any long-term data. Several techniques had been described for repair, but patch tracheoplasty dominated, and mortality rates were high.

At that time, relevant skills were distributed in such a way that individuals had to be consulted to manage specific problems. For example, endoscopic examination of the airway was largely done by ear, nose and throat (ENT) surgeons, cardiologists helped diagnose and manage cardiac issues,

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and the surgical reparative skills crossed boundaries. Intensive care was mandatory, but often seen as a "service" to other teams, and nursing was undervalued. Interventional radiology was embryonic, but increasingly seen to be relevant, and palliative care was only a consultative service. The interfaces between services were relatively formal; a *consultative* interface. As Reason pointed out many years ago (2), it is the interfaces which go wrong and lead to error because of failures in communication. Each discipline approached problems in its own way according to its own (often limited) experience.

Those of us involved in the care of these children decided that this was not good enough and ***everyone*** involved met in 2000 to work out how we might better deal with complex airway cases. It was the birth of the GOSH[1] Tracheal Team, and a fantastic meeting of minds. Several key decisions were made;

- The team should comprise all those coming into contact with such patients on a regular basis. Namely, but in no specific order of importance, cardiothoracic surgeons, ENT surgeons, interventional radiologists, specialist and intensive care unit (ICU) nurses, intensivists, respiratory physicians, pediatric general surgeons, anesthetists, diagnostic radiologists, speech therapists, physiotherapists, administrative staff, data managers, radiographers, cardiologists, and interested researchers and junior staff in training.
- A leadership structure was created.
- ALL referrals with complex airway problems would be reviewed by the Tracheal Team at a weekly multi-disciplinary team meeting (MDT).
- ALL relevant decisions about both individual patient care and overall strategy would be taken at the MDT, recorded and stored in a database.
- LSCTS would be treated by slide tracheoplasty on cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO), and where possible, cardiac lesions would be repaired at the same time.
- The team should learn to cross-skill to avoid delays to patient care. Specifically, this related to skills in fibreoptic bronchoscopy and balloon dilatation.
- All outcomes would be published, and attempts would be made over time to centralize care in the UK if results justified it.
- Links would be created with other interested specialists throughout the world.

Within just a few years we observed a significant increase in referral, improved outcomes and a dramatic reduction in the cost of care (3). Such single center reporting is prone to bias and uncertainty as to the cause of the improvement, but we maintain that all of the above decisions contributed in some way. We also noted greater cohesion, smoother decision making, constructive discussion and general happiness in the mode of working. Several other teams emerged simultaneously, notably in Chicago and Cincinnati, from different origins, and also commented on the value of integrated teamwork [see discussion at the end of (3)].

[1]GOSH = The Great Ormond Street Hospital for Children NHS Foundation Trust, London.

The growth of referral accelerated our learning, and the rate of improvement of results changed with it. In 2005–6 the team applied for, and was granted, national status by the National Health Service (NHS), becoming the sole center recognized for the treatment of complex airway disease in children. Since then growth has been continuous, with referrals coming from all over the world, bringing with it new challenges and increasing complexity of cases. Research blossomed, ranging from diagnostic techniques through to quality of life assessment, cell biology and transplantation. Our team was successful, and its teamwork "worked."

We are particularly proud of the way in which certain roles developed within the team. Specifically, and against some initial resistance by vested interests, the radiographer in our team was taught to undertake bronchoscopy and balloon dilatation, a skill which now makes her one of the world leaders in this field and a significant contributor to the literature. We will return to cross-skilling later.

THE THEORY

Is our experience unique, or are the consequences of good teamwork replicable? There has been a great deal of work undertaken about the importance of teamwork in surgery, and an excellent review of the relevant background for surgeons by the Royal College of Surgeons of England (RCS). This can be found at www.rcseng.ac.uk/surgeons/surgical-standards/professionalism-surgery/gsp. It is widely accepted that good teamwork improves clinical performance (4), patient outcomes (4, 5), and the well-being and retention of staff (6, 7). The effect on performance appears to be present even in a limited part of the patient journey, i.e., in the operating room (8). The RCS report highlights the point that teams come together to perform specific tasks, and thus the membership of the team must be capable of achieving that task *together*.

In high performing teams, members (6, 7):

- Understand their own and other members' roles and responsibilities
- Encourage contributions of all members and ensure that the views of new and junior members are taken into account
- Show respect for the role, expertise, competence and contributions of allied disciplines and healthcare providers.
- Respect the leadership of the team
- Have the shared goal of high-quality care for the patient
- Show a commitment to teamwork in the best interest of the patient
- Recognize they are important to the outcome of the task
- Feel confident to raise their voice or intervene.

It is wonderful when one finds oneself working in an effective team. Sadly, it is much more common to find oneself in a ***group.*** Giddings and Williamson (9) created a fascinating table which very clearly reveals the differences between a team and a group, which we reproduce here;

Team vs Group	
Decision by consensus	Decisions often not made
Disagreements examined and resolved	Unresolved disagreements
Objectives are well understood and accepted by the team	Objectives often not agreed
All members contribute ideas	Personal feelings are hidden
Self-examination of how the group is functioning occurs frequently	Discussions are avoided regarding how the group is functioning
Roles are understood by all members	Individuals tend to protect their role and their niche in the group
Shared leadership occurs on an as-needed basis	Leadership is appointed

Some key points emerge from this table, and these are reinforced by our own experience and from watching other teams/groups in action. Consensus, clarity of goals and understanding of roles may seem obvious, but the hiding of feelings is perhaps less so. How many of us can remember being in meetings in which half the people in the room do not contribute to the decision making, but can be found moaning in the corridor about the decision that was made? This reflects a dangerous lack of confidence in not speaking up (always dangerous for patients) and a lack of leadership in bringing everyone's views to the fore. It does not do, either, to have a leader foisted on a team; better to let the team choose its leader and be ready to change leadership as and when circumstances change (and they always will). Good teams are self-analytical; happy to consider their own effectiveness and to make changes rapidly when required.

We are all aware that teams can be dysfunctional and have probably experienced situations in which an individual has thrown the train of successful teamwork off the tracks, derailing the team. Another great table from Giddings and Williamson (9) [based on the work of Hogan and Hogan (10)] looks at the characteristics of strong team members and those who tend to derail (see below). A quick glance down the "derailer" column usually prompts memories of specific individuals by anyone who reads it. It is also highly reminiscent of some world leaders at the time of writing!

Strength	Derailer
Diligent	Perfectionist
Charming	Manipulative
Confident	Arrogant
Shrewd	Mistrustful
Focused	Passive aggressive
Careful	Cautious
Independent	Detached
Imaginative	Eccentric
Vivacious	Dramatic
Enthusiastic	Volatile
Dutiful	Dependent

Teams in healthcare are often larger than is ideal, and leadership is critical for effective performance. There is evidence that leadership clarity in healthcare environments improves both teamwork and innovation (11). But what good leadership actually really means is harder to define, and it is salutary to think about it from the team members' perspective as Goodwin discussed (12). Team members define the most common positive attributes of *healthcare* leaders to be; intelligence, ability, confidence, warmth and friendliness, benevolence, emotional stability, integrity and the abilities to delegate and communicate. There seems nothing to argue about in this list. In our view, these are attributes to which leaders of teams in our field should aspire, and by which they should be judged.

ISSUES SPECIFIC TO AIRWAY TEAMS

We have alluded to the wide membership of our own team in London, and it is worth considering why that should be necessary in a little more detail. As our team has evolved, the differences in core skills between the various members have become evident. This is best demonstrated by considering some examples.

- Within their discipline, ENT surgeons have developed skills in endoscopy (rigid and fibreoptic) and trans-endoscopic surgery. They are confident with very difficult airways and have had to work closely with specialist anesthetists to ensure the safety of their patients. They have specific technology and imaging experience and themselves often work in wider teams, for example in tracheostomy management. Culturally, ENT surgeons often receive direct referrals and stay in close contact with individual patients throughout the course of care, leading the management decisions.
- Cardiothoracic surgeons used to be just that, although it is becoming more common for cardiac and thoracic skills to be separated after appointment to the consultant (attending) staff, especially in pediatrics. Cardiac surgeons clearly are used to repairing the heart and blood vessels and to the use of cardiopulmonary bypass and ECMO. Both these latter can be lifesaving in severe airway problems. Cardiac surgeons are also used to working under time pressure because of the limitations of cardioplegic myocardial preservation, and to do so in a complex multi-disciplinary team of their own. Referrals usually are made to a team, via pediatric cardiologists and culturally almost all decisions are made in formal MDT meetings. Follow up of individual patients is often not directly with the surgeon, but by other members of the team, especially cardiologists and specialist nurses.
- Radiologists have a wonderful grasp of available technology, excellent dimensional interpretive skills and cross disciplines in their knowledge of diagnoses. In our world, this has led to developments in MR (flow dynamics), CT (4 D assessment of the airway), optical coherence tomography and advanced bronchography. The development of interventional radiology has involved them increasingly in therapy and

follow up including endoscopic or physiologic imaging. The development of balloon dilatation of airway and image-guided surgery has further expanded the role of radiology in airway disorders. Culturally, radiologists have rarely had longer term follow up as part of their job description, with referral on each occasion usually being on a "form—request" basis. They have always been deeply involved in MDTs from a diagnostic perspective, but increasingly they are crucial members of the team in determining therapeutic options and the role in decision making is continuous.

- Pediatric cardiologists are integral to service delivery. Eighty percent of our patients have had cardiovascular problems, often complex, and cardiac diagnosis and non-surgical intervention fall within the realm of the cardiologists. They have a huge role to play in deciding the *timing* of interventions, and involvement in the MDT is essential for complex patients.
- All the above groups have a tendency to be "activist," anxious to do something practical to intervene for the better. Such views need balancing, and the voice of the pediatric respiratory physician is crucial in this regard. It is often more valuable to the patient and his/her family to avoid surgery and the wisdom of someone who sees patients over time with detailed physiological and holistic assessment is of great importance to the team.
- The role of the nurse in the team cannot be underestimated. We have found it best to have a specialist "tracheal" nurse as the leader of the nursing team, and they have the front-line responsibility of communicating regularly with the families. It often comes as a surprise to surgeons that patients find them intimidating. This is rarely the case with nurses, who better grasp the wider needs of the patient and who take on a huge burden of communication with community services. Some of the most common complaints made against hospitals relate to difficulty in contacting the relevant person or failing to be called back with detail when promised. This is exactly what a well-trained and sympathetic nurse does well. Communication is everything.
- Administrative staff are needed to oil the wheels of the machine. The quality of service is dependent on them, and it is best to have them involved in all MDTs and team meetings. They ensure proper communication with other services and the family, and also help with maintaining the records and database, facilitating later research. They provide a great deal of support to families in practical, non-medical interactions with various authorities; many of these children have additional problems and appointments with hospital, school, social worker etc., all need to be coordinated to make a "one-stop shop" possible as often as possible. This is customer service. Some provide good service naturally, but it can be trained and should be expected.
- The remainder of the team comprises physio- and speech therapists, researchers and junior staff. Their role is variable, but they have much to offer; each will learn more about the patient and their voices should be heard.

Ross Brawn, the great Formula One manager, in describing what it takes to win a Formula One championship said (13)[2] that "everyone in the team should aspire to be World Champion at what they do." This is an important concept, reflecting disseminated ambition, strong leadership and a philosophy of excellence. Mostly, though it expresses the value of *every* member of a team in contributing to its success. People who fail to contribute to the team might better be employed elsewhere.

These are the human factors of surgery (14, 15), a field of study drawn from organizational psychology and of proven performance value in many industries, particularly aviation (16, 17). The team leaders should ensure that these human factors are monitored and appropriately maintained as time goes by. They need also to consider the impact of their own style (which can be measured) on others (18).

Most teams in medicine never have their team performance assessed. There are good examples of such assessment in certain specific areas, notably in anesthesia (19), emergency medicine (20), intensive care (21), and the operating room (22) in all of which there are good opportunities for simulation. The lack of assessment of complex teams with responsibilities for human lives is a situation that would not be allowed to exist in other high reliability organizations where regular human factors audit is regularly undertaken and is often part of licensing, for example the Line Operations Safety Audit to which commercial pilots and their teams are subject (16). Although not mandatory, it might be considered good governance for airway teams to subject themselves to such review.

THE EVOLUTION OF AIRWAY TEAMS

Medicine is changing fast. The impact of technology, particularly in imaging, minimally invasive surgery and communications has been immense and is accelerating. Changing patterns of referral change the demands on the team as time passes. Teams should not be static in such a context. Membership should be reviewed; the unnecessary should be redeployed and new relationships fostered as demands change.

In our own team two developments over the last decade have driven the need for change. The first has been the development of tracheal transplantation in various forms (23, 24) and the increased incidence of button battery injury (25). For the first, we needed to involve a wide range of scientists, adult research teams and international contacts. They worked at multiple institutions but were able to join our MDTs and research meetings thanks to video conferencing. Not only was this necessary to manage the individual patients, but it added skills we lacked, and which have subsequently become integral. Notably, the integration of clinicians caring for adults helped us better to plan the *transition* of care from pediatric to adult practice and ensure the lifelong follow up necessary to determine the value of any intervention (26). For the second, close collaboration was needed with general pediatric surgeons with primary responsibility (and understanding) of the esophagus and its surgery.

[2] Paraphrased.

Our team has thus changed its structure and now its name as a result. It is called the **aero-digestive team.** This reflects the changing pattern of work, and also how joint enterprise in a team format has meant that previously untried techniques are being developed to solve major problems (25), based on the respective skills of the team members. If close integration into team activities had not occurred, and if treatment was based on referral rather than working together as one team, these advances are unlikely to have been made. Once again, referrals are increasing, and the benefits of specialization are evident. The more you do, the better you get.

THE FUTURE

There is an old Chinese proverb[3] which goes "Those who have knowledge don't predict. Those who predict, don't have knowledge." Despite the dangers of prediction, some things are coming our way and we need to anticipate them. There is no doubt that the advent of artificial intelligence and machine learning will have an impact on decision making and outcome analysis. Data are critical to both, and there can be no excuse in the current era for incomplete or inaccurate data collection. Transparency is necessary, and no patient should be excluded from the databases, unless they specifically refuse consent. Asked correctly, and with the altruism of involvement in future benefit, refusal is rare.

Augmented reality is developing so fast that many of the interventional procedures we employ will be supported by these techniques, as too will surgical learning and patient understanding. Combining these developments will permit simulation and improved precision. The development of all though will need "volume." Research is unlikely to be funded for small or unstable teams.

Thus, there seems to be a significant rationale for centralizing pediatric airway care around teams of a certain, but undetermined, size and which embrace all the relevant skills. Such teams will benefit from international collaboration with similar teams, especially those of appropriate size. These teams exist and are contributing (27, 28). Research, transparency, partnership and co-operation are critical. As we said at the start of this paper, this is not a sport for individuals but for teams. Yet Brawn remains correct (13); if you want to win as a team, all the individuals must perform to the highest standard.

[3]Lao Tzu, 6th Century BC Chinese Poet.

AUTHOR CONTRIBUTIONS

ME wrote the first draft, and all the other authors contributed to the final text and approved it for publication.

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CASE REPORT
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Case Report: Resection of Giant Endotracheal Hamartoma by Electrosurgical Snaring via Fiberoptic Bronchoscopy in a 9-Year-Old Boy

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Endotracheal hamartomas are rarely encountered in children. The symptoms of endotracheal hamartoma may include cough, dyspnea, hemoptysis, chest pain, purulent sputum, and fever. The non-specific symptoms often result in a delayed diagnosis. Among the various treatments of this rare disease, surgical resection seems to be the most widely used, while endoscopic treatment is rarely described. Herein, we describe the case of a 9-year-old boy with an endotracheal hamartoma that was successfully excised by electrosurgical snaring via fiberoptic bronchoscopy (FB). The resection of select benign endotracheal tumors in children can be conducted using electrocautery, which can be regarded as an alternative therapy to bronchotomy.

Keywords: endotracheal lesions, hamartoma, therapeutic bronchoscopy, airway tumors, case report

INTRODUCTION

Benign lung tumors represent <1% of all lung tumors; among these, hamartomas have an incidence of 0.025–0.32% in the adult population (1). Although still an uncommon occurrence, hamartoma is the most common type of benign pulmonary tumor, accounting for an estimated 77% of benign lung nodules and 8% of solitary lung lesions (2, 3). Most hamartomas occur in the peripheral parenchyma, but have in rare cases been present in the trachea or bronchi. A previous study reported that the hamartoma was in an endobronchial location in only 1.4% of 215 patients with hamartomas (4). Although hamartomas may be found at any age, the age at presentation is mostly between 40 and 60 years; primary pulmonary, tracheal, or bronchial hamartomas are significantly rarer in the pediatric population (2, 5). The most frequent clinical symptoms of tracheal or endobronchial hamartomas are fever, cough, hemoptysis, purulent sputum, dyspnea, and pain due to tracheal or bronchial obstruction. Tracheal or endobronchial hamartomas are traditionally treated by thoracotomy with bronchotomy or lung resection. At present, the first-line widely recommended approach in adults is endoscopic treatment; however, similar treatments have rarely been reported in children (6). We herein describe a case in which electrosurgical snaring via fiberoptic bronchoscopy (FB) was applied to successfully resect a rare tracheal hamartoma in a young boy, avoiding the need for bronchotomy.

CASE PRESENTATION

A 9-year-old boy was referred to our hospital with a 20-day history of cough, stridor, and shortness of breath. He had showed a poor clinical response to conventional therapy with antibiotics and systemic steroids at a local hospital. He was previously healthy with no relevant family history. A computed tomography (CT) scan performed at a local hospital revealed a homogeneous mass obstructing the trachea. During preparation for rigid bronchoscopy (RB) at the local hospital, he was found to be intolerant to general anesthesia and his dyspnea exacerbated. He was transferred to our hospital immediately. On admission to our hospital, the patient appeared dyspneic and had a characteristic biphasic stridor, with a percutaneous oxygen saturation of 93% under mask oxygen inhalation, body temperature of 37.7°C, pulse rate of 162 beats/min, respiration rate of 34 breaths/min, and blood pressure of 127/74 mmHg.

On day 2, contrast-enhanced multidetector CT revealed a mass lesion with a fat density that was nearly totally obstructing the tracheal lumen (**Figure 1**). The multidisciplinary consensus was to proceed with bronchoscopy to obtain a definitive diagnosis to guide management and determine the prognosis. After being fully informed about the surgical options and possible complications related to different surgical modalities, the patient's parents elected to have the mass removed by an electrocautery snare with FB. A rigid bronchoscope (Karl Storz, Germany), argon plasma coagulation (APC) (ERBE VIO200D+APC2), cryotherapy (ERBOKRYO CA), and Holmium: YAG laser (Dahua DHL-1, China) were available if necessary. The parents also agreed that if the treatment failed, surgical resection would be carried out immediately. Written informed consent for the interventional procedures was obtained from the patient's parents.

The mass resection was performed on day 3. Pulmonologists, otolaryngologists, thoracic surgeons, anesthesiologists, and pediatric intensive care unit doctors were all in the operating room to ensure the success of the treatment and the safety of the patient. General anesthesia was induced with 8% sevoflurane. After the intravenous administration of 2 mg of midazolam, a laryngeal mask airway (LMA) was inserted to maintain an open airway. Intraoperatively, anesthesia was maintained with 3% sevoflurane. Based on the depth of anesthesia, 10 mg of pentazocine and 50 mg of propofol were intravenously administered intraoperatively. A swivel adapter was used to connect the proximal end of the laryngeal mask to the T-piece anesthesia system. A flexible fiberoptic bronchoscope (Olympus 260; external diameter: 4.9 mm, working channel: 2 mm) operated by an experienced pulmonologist was inserted via the swivel adapter. A large mass covered by smooth mucosa with a stalk was obstructing approximately 85% of the trachea in the mid-tracheal region (**Figure 2A**). A flexible 1.9-mm electrocautery snare (Olympus CD-6C-1) was then introduced through the working channel of the bronchoscope. After placing the loop of the snare around the base of the mass (**Figure 2B**), the electrocautery snare was used in blend mode at 30 W to cut and coagulate the base of the mass (**Figure 2C**). The mass was resected without evidence of bleeding or perforation (**Figure 2D**). The inspired oxygen concentration was maintained at 25% to avoid potential combustion during the interventional procedure. Due to the broad base of the mass, part of the remaining tissue at the root was removed with biopsy forceps to reduce the amount of residual tissue. Postoperatively, the patient recovered completely and was discharged home on day 8. The pathologic examination suggested that the mass was a tracheal hamartoma predominantly constituted of mature fat cells (**Figure 3**). The patient's condition remained stable for 1 year following the interventional therapy. The patient returned to the hospital for repeat chest CT examination and bronchoscopy at 1 year postoperatively (**Figure 4**). There was a slight protrusion at the position of the incision (**Figure 2E**).

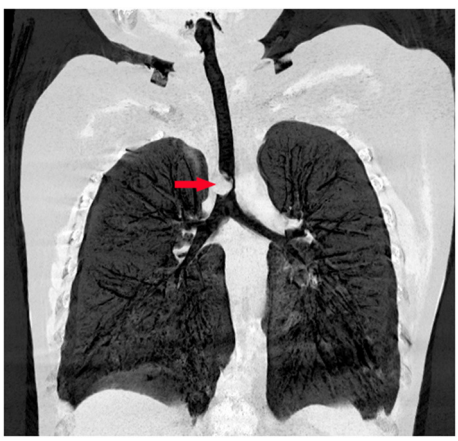

FIGURE 1 | Preoperative chest computed tomography reveals an endotracheal tumor nearly totally obstructing the tracheal lumen.

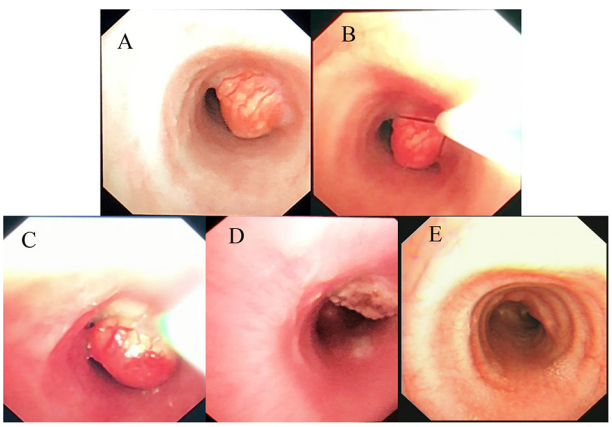

FIGURE 2 | (A) Fiberoptic bronchoscopy image of the large mass covered by smooth mucosa in the mid-tracheal region. **(B)** Placing the loop of the snare around the base of the mass. **(C)** The process of mass removal by electrocautery snare. **(D)** Most of the mass is removed by electrosurgical snaring under bronchoscopy. **(E)** Photograph showing a slight protrusion at the position of the incision at 1 year post-operatively.

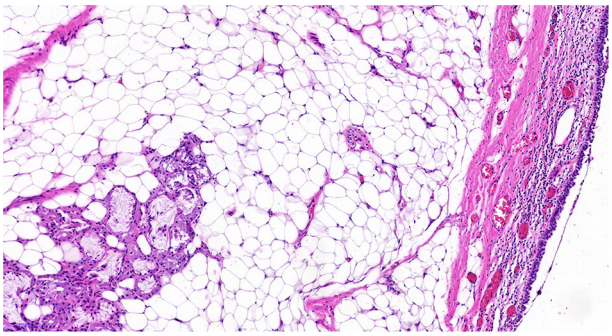

FIGURE 3 | The tumor was a hamartoma largely comprising mature fat cells.

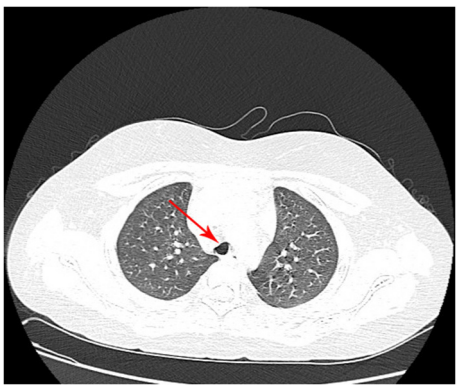

FIGURE 4 | Chest computed tomography at 1 year postoperatively shows that the anterior wall of the trachea has collapsed slightly.

DISCUSSION

Primary endobronchial and endotracheal tumors are uncommon in childhood. Of these, benign tumors consist of inflammatory pseudotumors (plasma cell granulomas), papillomas, hamartomas, mucus gland tumors, leiomyomas, and hemangiomas (7). Malignant tumors include mucoepidermoid carcinomas, carcinoids, adenoid cystic carcinomas, and bronchial adenomas (an obvious misnomer). The most common benign primary pulmonary tumors in children are inflammatory pseudotumors, followed by hamartomas (7).

Hamartomas in the lung are slow and abnormal growing neoplasms that are defined as a tumor-like malformation in which there is abnormal mixing of the normal components of the organ. In other words, a pulmonary hamartoma is a rare benign tumor that originates from the bronchial primitive mesenchymal tissue and can differentiate into various mature mesenchymal components (8). The histogenesis of hamartoma remains unclear. However, there are four etiologic theories: neoplasia, hyperplasia of a normal structure, congenital malformation, and response to inflammation. Both intraparenchymal and endobronchial hamartomas generally contain cartilage, bone, fat, and muscle tissue. Endobronchial hamartomas tend to have more fat than intraparenchymal hamartomas, which may be attributed to the relative abundance of fat in the tracheal walls as opposed to the lung parenchyma (9). This may partially explain why the mass in our patient was composed mainly of fatty tissue.

Patients with endotracheal hamartomas are generally asymptomatic, at least in the preocclusive early phase. The presenting symptoms including cough, dyspnea, hemoptysis, chest pain, purulent sputum, and fever are induced by tracheobronchial obstruction and can lead to recurrent pneumonia (10). As the clinical symptoms are not specific and depend on the size and localization of the tumor, endotracheal hamartomas are often misdiagnosed as more benign conditions, delaying definitive treatment (6, 11). Clinically, the differential diagnoses include aspirated foreign bodies, ectopic thyroid tissue, mucosal webs, cysts, as well as malignancies, including lipoma and lymphoma. With the popularization of CT and magnetic resonance imaging (MRI), it is often possible to determine a diagnosis or narrow the differential diagnosis list. Computed tomography (CT) is sensitive in diagnosing fat collections or calcifications. Fortunately, the hamartoma in our case mainly contained fat. In addition, the present patient was in a sitting breathing state because of airway obstruction caused by the hamartoma before surgery and could not tolerate lying flat for a long time for MRI examination. For these two reasons, we did not perform MRI. However, some hamartomas containing neither fat nor calcification are difficult to differentiate from malignant tumors. Magnetic resonance imaging is an excellent diagnostic tool for the evaluation of soft tissue tumors and has great diagnostic value for detecting the typical cleft-like structure in a pulmonary lesion when neither fat nor calcification is present on CT (12). Therefore, MRI may serve as an adjuvant or alternative diagnostic method to CT for thoracic lesions. However, the definitive diagnosis of hamartoma depends on the histological examination.

Surgical removal of the tumor in older patients should be done only when the tumor is symptomatic or if malignant transformation is suspected. In contrast to adults, peripheral and central hamartomas in children can cause marked symptoms and require prompt surgical removal. The traditional treatment is pneumonectomy or thoracotomy combined with bronchial resection in children (13). However, the first-line widely recommended therapy in adults is endoscopic treatment due to the benign nature of this disease with extremely rare malignant transformation and low recurrence rate (14). Our pediatric patient underwent successful airway recanalization via a flexible bronchoscope. However, due to the low incidence of this condition, experience with the endotracheal resection of hamartomas is relatively limited and there is no standard management for endotracheal hamartoma. Interventional bronchoscopic techniques utilized to manage airway lesions include electrosurgical snaring, APC, cryotherapy, and laser ablation. In the present case, the use of snare electrocautery minimized the bleeding risk by simultaneously cauterizing the base of the tumor during resection. Additionally, considering the unknown nature of the lesion at the time of presentation, we did not perform cryotherapy and APC to achieve hemostasis and destroy the residual tissue immediately after electrocautery. The bronchoscopic treatment options are dependent on the location

and characteristics of the airway lesion, physician's preference, expertise, and device availability (6).

Rigid bronchoscopy is probably the best conduit for managing endotracheal lesions, although bronchoscopy via a LMA is a viable option. However, it is important to note that the parents of pediatric patients tend to choose FB. Because the patient could not tolerate anesthesia at the local hospital, he was unable to undergo RB there. Therefore, we chose to use bronchoscopy via a LMA rather than RB. The advantage of LMA general anesthesia is that it enables control of the patient's breathing and provides a large space for endoscopic operation. If it had been difficult to remove the tumor under FB, we would have attempted mechanical debulking under RB. If the patient had not been able to tolerate laryngeal mask anesthesia, we would have attempted to resect the mass via FB under tracheal intubation anesthesia. If we had been unable to remove the mass via FB under tracheal intubation anesthesia, the thoracic surgeon would have performed an open thoracotomy. The extracorporeal membrane oxygenation team was ready to provide emergency treatment if the vital signs became unstable. The management of pulmonary hamartoma might be highly center- and patient-dependent. There is no gold standard due to the rare nature of the lesion and lack of uniformity in expertise among centers in managing such cases. Therefore, a large prospective clinical trial is needed.

The electrocautery snare has the ability to sever a large mass quickly with concomitant hemostasis. The advantages of electrosurgery via FB are the provision of larger tissue specimens for more accurate histological diagnosis, recanalization of the involved airway, better assessment of the tumor base, more accurate surgical planning, stabilization of the patient to enable them to undergo surgery in a better general condition, and minimization of the bleeding risk by simultaneous cauterization of the base of the tumor during resection. Despite the partial residual tissue (**Figure 2D**), our patient's symptoms were relieved immediately after electrocautery, indicating that electrosurgical snaring is a potentially useful method with which to manage endotracheal hamartoma. Once the emergency situation was handled, the next step was to evaluate the need for further management depending on the histopathology. Although we advised further bronchoscopic debulking (e.g., cryotherapy and APC) of the residual mass (**Figure 2D**) based on the histopathologic result, the parents chose serial clinic visits, imaging, and airway inspections rather than bronchoscopic debulking. The patient remained recurrence- and symptom-free and the airway remained patent following bronchoscopic surveillance at the 1-year follow-up (**Figures 2E**, **4**); this indicates that the outcome of electrosurgical snaring via FB for tracheal hamartoma appears to be satisfactory, although the long-term survival remains to be assessed. Hence, our experience suggests that bronchoscopic treatment can be considered as a bridging therapy to definitive treatment.

As hamartoma is a benign neoplasm, endoscopic treatment is now widely recommended as the first-line approach. Theoretically, hamartoma can be managed endoscopically in all age groups. However, the diameter of the electrosurgical snare and the working channel of the flexible bronchoscope limit the wide application of this technique. The diameter of the flexible electrocautery snare is 1.9 mm, which can pass through the working channel of the flexible bronchoscope BF-P260 (external diameter: 4.0 mm, working channel: 2.0 mm). As the smallest flexible bronchoscope with a 2.0-mm working channel, our experience suggests that the Olympus P260 can be used in children older than 2 years. Thus, electrosurgical snaring might be useful for endoscopically managing tumors in children $\geq$2 years.

The common complications of electrosurgical snaring include bleeding, perforation, and endotracheal burns (15). The main reason for bleeding during electrocautery snaring is that the snare shrinks too fast when cutting the tumor, which makes the electrical cut a simple mechanical cut, leading to tumor tearing and bleeding. The optimal strategy to prevent bleeding is to cut the mass slowly, so that there is enough time to cauterize the basal tissue while cutting the mass, and the basal tissue is coagulated and denatured. The main reason for airway wall perforation is that the direction of electric cutting deviates from the direction of the bronchus during the treatment process. Therefore, a good visual field should be maintained to avoid the cutting angle deviating from the direction of the bronchus. Using APC cauterization or cryotherapy at the mass root can reduce the risk of tumor recurrence. In the present case, we did not perform mass root interventional therapy because the airway obstruction was relieved after mass resection via the electrocautery snare, and the pathological diagnosis was not clear at that time. Although a small part of the tumor remained after resection, the patient had no symptoms, and the parents were not willing to consent to further thoracotomy. If the tumor continues to grow, thoracotomy is the best option.

Although interventional bronchoscopy is a mature technique in adults, it is seldom used in children. However, our case suggests that under careful preparation, interventional bronchoscopy can be safe and beneficial in pediatric patients.

CONCLUSION

Endotracheal hamartoma is a rare benign tumor, and bronchoscopic therapy is recommended as the first-line treatment, although surgical resection may be necessary under certain conditions. Clinicians should consider the presence of tracheal lesions such as hamartomas in pediatric patients who obtain no significant improvement of respiratory symptoms after conventional treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

and institutional requirements. The patients/participants (legal guardian/next of kin) provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZC supervised research work. LW and SL participated in collecting information of this case and searched for literatures. All authors participated in the interpretation of the data, contributed to the article, and approved the submitted version.

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CASE REPORT
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Congenital Bronchobiliary Fistula: A Case Report and Literature Review

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Congenital bronchobiliary fistula (CBBF) is a rare disease. Children with CBBF mostly have atypical clinical manifestations that can be easily missed. We report a case of a child with CBBF who was diagnosed with fistulography with the help of an endobronchial blocker and a fiberoptic bronchoscope. The CBBF was successfully removed by thoracoscopic surgery.

Keywords: congenital bronchobiliary fistula, bronchoscope, endobronchial blocker, fistulography, thoracoscopic surgery

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INTRODUCTION

Congenital bronchobiliary fistula (CBBF) is a rare disease, which was first reported by Neuhauser et al. (1). It is a rare developmental anomaly, i.e., fistula between the respiratory and biliary tract. Its clinical manifestations are recurrent and persistent refractory pulmonary inflammation. We reported a 2-year-old boy with CBBF, who was successfully diagnosed with fistulography and treated by thoracoscopic surgery.

CASE PRESENTATION

A 2-year-old boy was hospitalized in our center for recurrent pneumonia. He was hospitalized three times for pneumonia in the past 6 months. The main symptom was cough. The child is too young to cough sputum out. There was no typical yellow-greenish sputum in the period of pneumonia. There was also no cyanosis, respiratory distress, or jaundice. Chest x-ray showed chronic inflammatory changes on the right side at the beginning of the disease. Application of antibiotics and drug-aerosol inhalation can relieve cough symptoms. Chest CT showed multiple patchy hyperdense shadows in both lungs. The 3D-CT reconstruction showed that the wall of the right main bronchus has a conical cleft-like protrusion with the end pointing downward last time (**Figure 1A**).

In the catheter room, fiberoptic bronchoscopy and bronchography were performed at the same time. Under general anesthesia, a standard 5.5-mm-inner diameter (ID) endotracheal tube (ETT) without cuffed was successfully inserted into the trachea. A multiport airway adapter (Tappa, Common type, EBT0105) was used to connect endotracheal intubation (**Figure 2**) (2). An electronic fiberoptic bronchoscope was inserted into the trachea through the multiport airway adapter, whose outside diameter is 2.8 mm. We can see yellow secretions attached to the glottis and trachea through the fiberoptic bronchoscope. An abnormal opening was found at the level of the tracheal carina, and yellow secretions could be seen at the opening (**Figure 3A**). The pediatric endobronchial blocker (5-Fr) was inserted into the tube through the multiport airway adapter. Different models of endobronchial blockers have clear matching endotracheal intubation diameter and fiberoptic bronchoscope specification (**Table 1**). With the assistance of an electronic fiber bronchoscope, the endobronchial blocker was inserted into the fistula (**Figures 3B–D**). Two milliliters of gas was injected into the endobronchial blocker through the end lateral hole, and

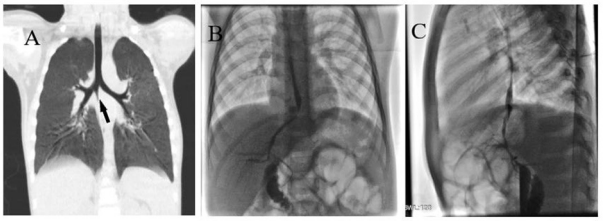

FIGURE 1 | (A) Right main bronchus wall with conical cleft-like protrusion (black arrow). **(B)** Anteroposterior angiography of BBF. **(C)** Lateral angiography of BBF.

the cuff of the endobronchial blocker was filled to close the fistula. Iodixanol was used as the contrast agent. A 20-ml syringe was used to connect the exhaust pipe of the endobronchial blocker to inject the fistula, and DSA was performed at the same time. It can be seen that the contrast medium is connected to the left hepatic duct through the esophageal hiatus, and the contrast medium sequentially fills the left intrahepatic bile duct, the right intrahepatic bile duct, the common hepatic duct, the common bile duct, the gallbladder, and the duodenum (**Figures 1B,C**). No other biliary malformation was found. Ultrasound examination of the liver and gallbladder showed no abnormality. The examination of hydatidosis and other parasites was normal. By way of aspiration of intratracheal lavage fluid examination, the total bile acid was found to be 306.20 μmol/L. Esophagotracheal fistula was not found by upper gastrointestinal angiography.

We discussed the diagnosis and treatment of CBBF with the guardian of the child and signed the informed consent for the operation. The CBBF was cut off and sutured by video-assisted minimally invasive thoracopic surgery. Two endobronchial blockers were used. For one-lung ventilation, one endobronchial blocker was inserted into the right main bronchus under bronchoscope guidance before intubation. After that, a standard 5.5-mm ETT without cuff was inserted into the trachea and connected to the multiport airway adapter. Under bronchoscope guidance, the second endobronchial blocker was inserted into the CBBF through the multiport airway adapter and ETT. The right posterior axillary line in the sixth intercostal space was used as the observation hole, and a 30° 5-mm thoracoscope was inserted. The fourth intercostal space in the right anterior axillary line and the seventh intercostal space in the middle axillary line were the operation holes. A 6-mm-diameter fistula was found at the beginning of the right main bronchus below the tracheal carina (**Figure 4A**). The fistula runs down the right side of the spine and passes through the diaphragm. By shaking the endobronchial blocker in the fistula, the BBF shaking can be seen under the thoracoscope. The fistula was fully exposed and the whole course of the fistula was free intrathoracic (**Figure 4B**). After double ligation with No. 10 mousse thread at both ends (**Figure 4C**), the fistula was double clamped with a hemolock clamp, and the fistula was removed with an ultrasonic knife (**Figure 4D**). Lastly, the thoracic drainage tube was placed through the seventh intercostal operation hole. The operation lasted 105 min. Tracheal intubation was removed 1 h after the operation. The excised fistula was sent for pathological examination. Microscopically, the specimen presented as a tubular structure of cartilage and muscle, lined with squamous and pseudostratified ciliated columnar epithelial mucosa and submucosal glands. It was considered as tracheal malformation. The lung shadow disappeared, which was demonstrated by chest CT after 6 months of the operation.

DISCUSSION

CBBF is associated with abnormal embryonic development. Its symptoms can occur from newborn to adult (3, 4). The severity of CBBF is different, which is related to the diameter of the fistula and whether combined with bile tract malformation. The earlier the symptoms appear, the more severe the condition is. This patient began to cough repeatedly at 2 years old but did not expectorate typical yellow-greenish sputum. Typical yellow-greenish sputum is rarely seen in infants. Infants also cannot describe whether the sputum is bitter or not. Therefore, it is easy to miss a diagnosis in infancy. If infants show recurrent pneumonia, yellow-greenish sputum can be seen during sputum suction, and cone-shaped fissure-like protrusion can be seen on chest 3D-CT reconstruction. In this situation, CBBF should be suspected, and relevant examinations should be further improved to make a definite diagnosis.

There are various diagnostic methods for CBBF. The increase of total bile acids in sputum or intratracheal lavage fluid is helpful for the diagnosis of CBBF. Chest CT scan and 3D-CT reconstruction can show the abnormal branches of the trachea. It is difficult to directly show the whole shape of the fistula, but it can evaluate the severity of pulmonary inflammation and guide whether the lobectomy should be performed at the same time. Abdominal CT examination can diagnose primary diseases such as liver abscess and bile duct stones. In addition, some patients can see a gas shadow in the bile duct. Abnormal branches of the trachea and gas shadow in the bile duct are important indirect signs of BBF. In this case, the abnormal branch of the trachea was found in the previous chest CT examination. It was ignored and diagnosis was missed. Percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) can show the origin and course of the fistula. In addition, it can also confirm whether there are other bile duct malformations. At present, PTC and ERCP are the main methods for the diagnosis of acquired bronchobiliary fistula (ABBF) in adults (5). Because the PTC and ERCP are complex and traumatic, it is not widely carried out in children (6, 7). Contrast-enhanced magnetic resonance cholangiography can show the anatomy of the biliary tract and provide physiological or pathological bile flow function information. Compared with conventional magnetic resonance cholangiopancreatography (MRCP), contrast-enhanced magnetic resonance cholangiopancreatography has more obvious diagnostic advantages. However, it needs longer operation time and higher technical requirements (8). Bronchoscopy is the first choice for the diagnosis of CBBF.

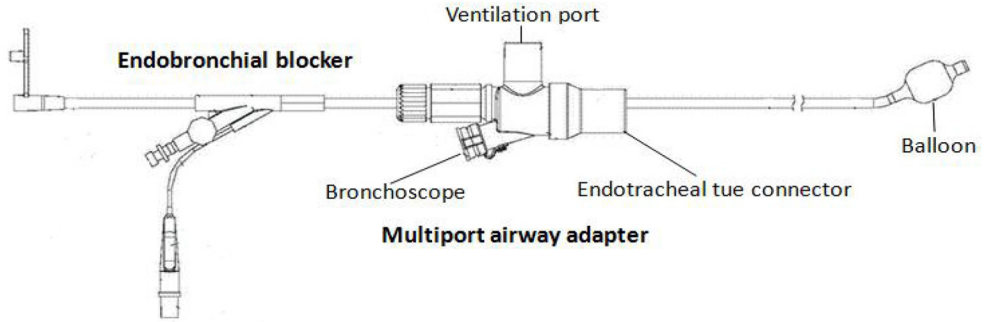

FIGURE 2 | The pediatric endobronchial blocker system.

Through the bronchoscope, we can see the yellow-green liquid overflowing from the fistula, and it will still overflow again after lavage. The bile acid test of lavage fluid is positive, which has an important diagnostic value. The bronchoscopy cannot show the whole course of the fistula. Bronchography can show the course of CBBF. Traditional bronchography involves the catheter being inserted into the trachea through the biopsy hole of the bronchoscope and a contrast agent is injected (9, 10). Li et al. (9) retrospectively analyzed 44 cases of CBBF. It showed that the orifice of CBBF was near the tracheal carina, with 45.4% opening in the right main bronchus, 43.2% opening in the tracheal carina, and 11.4% opening in the left main bronchus. Because the position of the fistula is very high, the contrast medium fistulography is easy to flow to the lower bronchi and alveoli. If the fistula is thin, the fistula is often not displayed, let alone the bile duct. We used the endobronchial blocker to block the orifice of CBBF. The whole shape and course of the BBF could be displayed by injecting contrast agents under x-ray fluoroscopy. There are three advantages to increase the injection pressure of the contrast agents and prolong fluoroscopy time. First of all, in addition to clearly showing the fistula, the left intrahepatic bile duct, the right intrahepatic bile duct, the common hepatic duct, the common bile duct, the gallbladder, and the duodenum can also be displayed in sequence. To determine whether there is a biliary malformation, ERCP cholangiography is not necessary. It can provide an important reference for the choice of surgical methods. Secondly, CBBF can be located by anteroposterior and lateral fluoroscopy. It can help to select the position of the observation hole and the operation hole for the thoracoscopic surgery. Finally, the CBBF tracheal fistula was occluded for angiography, which can avoid contrast media reflux to the bronchus and alveoli.

The main treatment method of CBBF is operation, which depends on the location of the fistula and whether it is combined with other liver and biliary diseases. It includes fistulectomy and plugging under bronchoscopic guidance. In case of CBBF with bile duct malformation, absence of common bile duct, abnormal bile intestinal drainage, and so on, fistula jejunum Roux-en-Y anastomosis, hilar jejunum anastomosis, and gallbladder jejunum anastomosis, among others, are feasible

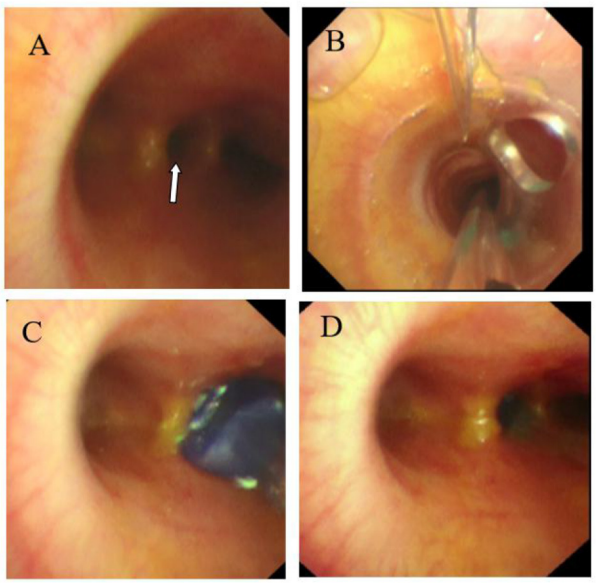

FIGURE 3 | (A) Abnormal opening of the tracheal carina (white arrow). **(B)** Endobronchial blocker enter into the trachea. **(C)** Endobronchial blocker enter into the fistula. **(D)** The endobronchial blocker was inflated and fixed after entering the fistula.

to fully drain bile and avoid fistula recurrence (11–13). The plugging of the fistula under bronchoscope guidance has the advantages of less trauma and quick recovery. At present, it is mainly used in adult ABBF, and there are few reports in children (14–19). Video-assisted thoracoscopic surgery in the treatment of CBBF can provide an unparalleled surgical vision compared to thoracotomy. In addition, it has less trauma and faster postoperative recovery. However, it is rarely reported in children (20–22). The CBBF-ectomy of this case is through mini-incision by video-assisted thoracoscopy surgery. One-lung ventilation was performed by an endobronchial blocker. The BBF was cut off and sutured. At present, the commonly used single lung ventilation technology includes double-lumen bronchial catheter ventilation and endobronchial blocker blocking one

TABLE 1 | Different models of endobronchial blocker have clear matching endotracheal intubation diameter and fiberoptic bronchoscope specification.

Endobronchial blocker (Fr)		5			7			9	
Endotracheal intubation (mm)	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5
Bronchoscope (mm)	2.2		2.8		3.5			4.0	

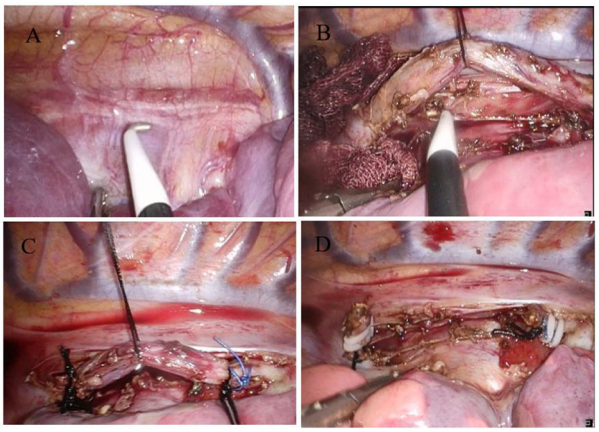

FIGURE 4 | Video-assisted thoracoscopic surgery to cut and suture the fistula. **(A)** CBBF was detected. **(B)** Free CBBF. **(C)** Ligation of CBBF. **(D)** CBBF was cut and sutured.

side of the main bronchus (23, 24). The smallest double-lumen bronchus tube is 26F. For children under 8 years old, one-lung ventilation with a double-lumen bronchus tube is impossible. The peripheral diameter of an endobronchial blocker is significantly smaller than a double-lumen endobronchial tube. The applicable age range of the endobronchial blocker is wider than the double-lumen endobronchial tube (2, 25, 26). The bronchial orifice of the CBBF was occluded by an endobronchial blocker. It can prevent bile acid from reflux into the trachea when squeezing the fistula during operation. Then, it can avoid asphyxia and chemical inflammatory injury of the lung. The course of the BBF should be confirmed before resection. We can confirm the target fistula along the abnormal branch of the trachea. Besides, the fistula can be seen by shaking the endobronchial blocker.

In conclusion, if the patient has recurrent cough and refractory pneumonia, we should be alert to CBBF. The airway reconstruction can show abnormal tracheal branches and abdominal CT can find a gas shadow in the liver. Bronchography can make a definite diagnosis of CBBF with the help of the bronchoscope and endobronchial blocker. The application of a double endobronchial blocker during operation can not only effectively implement one-lung ventilation for children but also help to determine the course of BBF and prevent bile acid reflux to the lung. It is a simple, feasible, accurate, and reliable diagnostic and treatment method to block the fistula with an endobronchial blocker. Video-assisted thoracoscopic surgery is a safe (with minimal trauma) and effective way to cut off the fistula.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Qingdao Women and Children's Hospital (QFFLL-YJ-2021-07). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

ZB was responsible for data interpretation, drafting of the manuscript, and approval of the final version to be published. RC, PX, YR, and KH were responsible for the study concept, data collection and interpretation, revision of the manuscript, and approval of the final version to be published. All authors read and approved the final manuscript.

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