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Neonates with Tongue-Based Airway Obstruction: A Systematic Review

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Abstract

Objective. In this systematic review, the authors summarize the current evidence in the literature regarding diagnosis, treatment, and long-term outcomes in neonates with tongue-based airway obstruction (TBAO) and assess the level of evidence of included studies.

Data Sources. The terms *Pierre Robin syndrome/sequence, micrognathia, retrognathia*, and *cleft palate* were combined with *airway obstruction, treatment, tongue-lip plication*, and *osteogenesis distraction* to perform an Ovid literature search, yielding 341 references. The authors excluded references containing patients with isolated choanal/nasal obstruction, patients older than 12 months, and expert opinion papers, yielding 126 articles.

Review Methods. The authors searched 3 electronic databases and reference lists of existing reviews from 1980 to October 2010 for articles pertaining to the diagnosis, treatment, and outcomes of TBAO. Reviewers assigned a level of evidence score based on Oxford's Centre for Evidence Based Medicine scoring system and recorded relevant information.

Results. Most studies were case studies and single-center findings. The lack of standardization of diagnostic and treatment protocols and the heterogeneity of cohorts both within and between studies precluded a meta-analysis. There was little evidence beyond expert opinion and single-center evaluation regarding diagnosis, treatment, and long-term outcomes of neonates with TBAO.

Conclusions. The variability in the phenotype of the cohorts studied and the absence of standardized indications for intervention preclude deriving any definitive conclusions regarding diagnostic tools to evaluate this patient population, treatment choices, or long-term outcomes. A coordinated multicenter study with a standardized diagnostic and treatment algorithm is recommended to develop evidence for the diagnosis and treatment of neonates with TBAO.

Keywords

tongue-based airway obstruction, Pierre Robin sequence, micrognathia, retrognathia, systematic review

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Neonates with tongue-based airway obstruction (TBAO) present a diagnostic and therapeutic challenge. Patients with TBAO have an upper airway obstruction that is related to the tongue rather than upper airway obstruction involving choanal or other isolated nasal or palatal obstructions. A significant portion of neonates with TBAO fall under the category of Pierre Robin sequence (PRS), first described by Pierre Robin in 1923 as a triad of micrognathia, upper airway obstruction, and glossoptosis.[1] However, not all newborns with TBAO have PRS. Neonates with TBAO can present with varying degrees of feeding difficulties and respiratory distress secondary to posterior displacement of the tongue, abnormal tongue posture, and retrognathia.[2] The severity of airway obstruction and feeding difficulty can be compounded by the presence of other congenital anomalies. Although many different diagnostic and management algorithms have been proposed for the treatment of this patient population, there are no evidence-based guidelines. The difficulty in developing guidelines arises for several reasons: (1) the phenotype of neonates with TBAO is highly variable, presenting as an isolated entity or as part of a syndrome along with multiple other congenital anomalies; (2) identifying and quantifying TBAO is difficult; and (3) a subset of neonates with TBAO will resolve their upper airway obstruction with time and mandibular growth and therefore

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Table 1. Database and Search Terms Used to Identify Relevant Articles

Database	Date Searched	Search Terms
Ovid Medline	1980 to October 2010	MeSH terms: Pierre Robin syndrome/Pierre Robin sequence (exploded), micrognathia (exploded), retrognathia (exploded), or cleft palate (exploded) combined with airway obstruction/upper airway obstruction (exploded), treatment (exploded), tongue-lip plication (exploded), osteogenesis distraction (exploded)
CINAHL	1997 to October 2010	Free text keywords: Robin sequence, Pierre Robin sequence, Robin sequence etiology, Robin sequence definition, Robin sequence prenatal diagnosis, mandibular distraction, tongue-lip adhesion/plication, micrognathia prenatal diagnosis, Robin syndrome, micrognathia, retrognathia, glossoptosis
Cochrane Reviews	1980 to October 2010	Pierre Robin sequence, upper airway obstruction

need only temporizing measures. The objective of this systematic review of the literature is to assess the level of available evidence for the diagnosis, treatment, and long-term outcomes of neonates with TBAO.

Methods

Data Sources

We performed a literature search of 3 major electronic databases: Ovid Medline 1980 to October 2010, CINAHL 1997 to October 2010, and Cochrane Database of Systematic Reviews. The electronic search was further supplemented by pertinent articles identified in the reference lists of existing reviews and the articles initially identified in the electronic search.

Study Selection

The search terms *Pierre Robin syndrome/Pierre Robin sequence*, *micrognathia*, *retrognathia*, and *cleft palate* combined with *airway obstruction/upper airway*, *treatment*, *tongue-lip plication*, and *osteogenesis distraction* were used (**Table 1**). Journal articles references were managed using EndNote (Thomson Reuters, Philadelphia, Pennsylvania). The article titles and abstracts were reviewed for eligibility. Each eligible article was reviewed by 2 authors of this systematic review. For each article, the reviewers assigned a level of evidence score (1-5) based on Oxford's Centre for Evidence Based Medicine scoring system and recorded relevant information.[3] A score of 1 is the highest score and is used for randomized controlled trials, and a score of 5 is used for case reports. A complete explanation of the 5 levels is detailed in **Table 2**.[3,4] Inclusion criteria included articles written in the English language, published between 1980 and October 2010, addressing TBAO in infants younger than 12 months of age. Case reports, case series, and cohort studies were included. Studies of patients with isolated choanal or nasal obstruction, as well as those with anatomic obstructions arising from the hard or soft palate, were excluded from the review. Studies containing only expert opinion were excluded unless patient-specific outcome data were included.

Definitions

Studies that included patients with retrognathia or micrognathia and glossoptosis with cleft palate and/or airway obstruction were described as "isolated PRS." Studies that included patients with a known syndrome associated with PRS were described as "syndromic PRS." Studies that included patients with other congenital anomalies but no defined syndrome were described as "unique PRS." This standard was used by Smith and Senders[5] to describe their patient population. Studies that did not describe the PRS patient population were described as "PRS unspecified." Studies that included interventions with prone positioning, palatal obturators, and nasopharyngeal or laryngeal mask airway were described as "conservative management."

Table 2. Level of Evidence (Oxford Centre for Evidence Based Medicine)[3]

Level	Type of Study
1	Systematic reviews, meta-analyses, randomized controlled trials
2	Nonrandom prospective controlled trial, cohort study
3	Case-control studies
4	Case series
5	Expert opinion, case report

Data Analysis

Statistical data analysis was not performed because most articles were level 4 or below, and the heterogeneity of the 13 higher level of evidence studies precluded direct comparison.

Results

A flowchart describing article inclusion and exclusion is shown (**Figure 1**). The abstracts of 341 articles identified during the initial search process were reviewed; 151 of these appeared to meet the inclusion criteria and were reviewed in their entirety. Following evaluation of the full text, a further 25 were excluded; information from the remaining 126 studies was abstracted for data. The findings from included papers are summarized in the appendix (available at otojournal.org).

Diagnosis

Glossoptosis is the most common cause of tongue-based upper airway obstruction in infants and is most commonly associated with PRS.[6] The criteria used to make this diagnosis

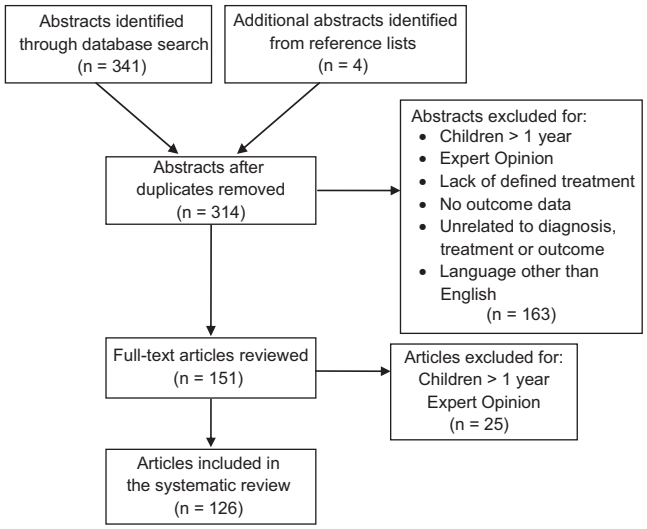

Figure 1. Flow diagram for article selection for inclusion in the review.

are critical to identifying infants at risk for upper airway obstruction. However, there are varied opinions regarding the diagnosis of Robin sequence. The original patients described by Pierre Robin had micrognathia, glossoptosis, and obstructive apnea.[1] Because various patients with Robin sequence have cleft palate as a concomitant finding, many clinicians have come to define PRS as consisting of micrognathia, glossoptosis, and cleft palate.[6,7] Multiple studies provide descriptive physical information to define the neonate with TBAO, but the description is diverse based on study population.[7-15]

Syndromes are an underlying feature of PRS in 27% to 82% of children and are found in a significant portion of those with TBAO.[7,15-19] In 7 studies of patients with PRS, the most common syndrome identified was Stickler syndrome, followed by velocardiofacial syndrome, hemifacial microsomia (oculo-auriculo-vertebral dysplasia), Treacher Collins syndrome, fetal alcohol spectrum disorder, and chromosome anomalies.[7,9,11,15,17,18,20]

In this systematic review, 59 studies that included criteria or approaches for diagnosis of TBAO were evaluated. None used objective criteria beyond clinical experience, subjective assessment of a short mandible, or respiratory distress. Morphometric criteria were used in 5 studies as an assessment criterion.[10,21-24] However, these were applied to patient cohorts already assigned a diagnosis of PRS and were not necessarily useful for prospective evaluation and diagnosis. Overall, no studies incorporating objective diagnostic criteria for TBAO to guide evaluation of medical or surgical management strategies could be identified.

Management

There were a total of 84 studies reviewed related to the management of neonate with TBAO. The reviewed literature (see the appendix) is full of case series of successful management of neonates with TBAO using many modalities. However, a critical appraisal of the literature reveals a lack of substantiated evidence. Of the 84 studies listed in the appendix related to management and reviewed according to these criteria, only 1 randomized controlled trial exists.[25] The remaining literature comprises case series and case reports based on level 4 and 5 data. We describe findings in more detail below. The data presented in **Table 3** are a summary compiled from data systematically extracted by readers for both the inherent advantages and disadvantages of each technique and included the most commonly cited complications.

Conservative Management

Conservative management has been defined as those patients who were managed successfully without surgical intervention. The literature describes prone positioning, nasal pharyngeal or laryngeal mask airway, suction drinking plate, or palatal obturators as conservative management.

Surgical intervention for neonates with upper airway obstruction has been indicated when conservative measures have failed to alleviate obstruction of the airway. Twenty-three studies have reported outcomes with conservative measures. Seventeen studies reported that most of their study population was managed successfully with only conservative measures.* Most of the studies include a mixed population of patients (isolated PRS, syndromic PRS, unique PRS, or other), but 4 studies reported more surgical intervention was needed in the syndromic or unique PRS population,[5,20,30,38] and 2 studies reported more success with conservative management in the isolated PRS population.[5,39] However, in contrast to this, Evans et al[15] reported no statistical difference in the frequency of surgery between syndromic and nonsyndromic patients ($P = .264$). Buchenau et al[25] reported success in a prospective randomized controlled trial of 11 patients using a palatal obturator with oropharyngeal extensions, but this single prospective randomized controlled trial is limited by its small treatment population and potential for a crossover effect.

Indication for Surgery

Eight studies describe the indications for surgical intervention in their study population.[20,34,40-45] These are all level 4 or 5 studies and vary with detail of criteria for surgical intervention from comprehensive evaluations to statements designating that the patient was refractory to conservative management.

Mandibular Distraction

Mandibular distraction (MD) and tongue-lip adhesion (TLA) are the most common surgical interventions described in the recent literature for treatment of neonates with TBAO. Despite emerging data reporting the safety and efficacy of MD in large retrospective case series, no randomized controlled trials or cohort or case control studies are currently available. Multiple authors have documented its success in improving polysomnography (PSG) data[41,45-48] and, more specifically, the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI).[42,49,50] Another published measure of success is avoidance of a tracheostomy or decannulation of a

*References 5, 12, 14, 15, 17, 20, 26-37.

Table 3. Management of TBAO Advantages and Disadvantages

Intervention	Advantages	Disadvantages	References
Mandibular traction	No osteotomies Relieves dyspnea Improved feeding	Laceration of mandibular symphysis Temporomandibular joint (TMJ) ankylosis	34
Nasopharyngeal airway and modifications	Potentially avoids surgery Temporarily corrects and bypasses anomalous anatomy Improves feeding	Requires frequent device modification May increase airway resistance Risk of device displacement Variable success rates Patient discomfort	20, 26, 32, 35, 36, 67, 69, 82, 108, 116, 126
Palatal obturators and modifications	Temporarily corrects and bypasses anomalous anatomy Improves feeding	Requires frequent device modification Risk of device displacement Variable success rates Palatal tenderness Technical expertise with fabrication needed	12, 25, 99
Tongue-lip adhesion (TLA)	Temporarily bypasses obstruction to create stable airway Straightforward postoperative care	Requires further operations Variable success rates Difficulties feeding Scarring Wound dehiscence Disruption of tooth eruption Submaxillary duct obstruction	13-15, 17, 28, 30, 55-58, 68, 70, 73
Transmandibular K-wire	Minimally invasive Temporarily bypasses anomalous anatomy	Displacement of wire Infection Laceration of tongue Nerve damage	61
Subperiosteal release	Minimally invasive Improves feeding Improves speech Addresses anomalous tightened musculature	Variable success rates Need for intubation/continuous positive airway pressure postoperatively Cutaneous scarring Infection Growth disturbance	28, 40, 62-64
Mandibular distraction (MD)	Corrects micrognathia Creates stable airway Expands soft tissue Avoids bone graft Improves apneic events Improves feeding	Invasive Variability of practice and technique Pin migration Requires further surgery Cyst formation Device failure or migration Scarring Nerve injury Infection Malocclusion or tooth bud disturbance Parotid duct injury Growth disturbance Spinal cord injury TMJ ankylosis or trismus	22, 27, 33, 41-48, 50-54, 71, 74, 76, 94, 96, 103, 111, 112, 122
Tracheostomy	Gold standard for airway stabilization Bypasses airway obstruction	Failure to correct anatomic cause of obstruction Accidental decannulation or dislodgement Tracheostomy tube plugging Aspiration Esophageal injury Suprastomal granuloma formation Bleeding Infection Tracheal stenosis or injury Tracheocutaneous fistula Mortality	67, 68, 77

tracheostomy, and several studies have reported this finding.[41,43,44,46,50-52] Other studies have reported a reduction in the need for tracheostomy secondary to the MD procedure.[†] Of the 29 articles that met inclusion criteria for this systematic review, all data on MD appear in level 4 or 5 studies, with no prospective data. In the largest retrospective series to date, Shetye et al[54] reported a 5% major complication rate, 27% minor complication rate, and overall complication rate of 52%. Additional shortcomings of the literature about MD are wide variations in practice, numerous intra- and postoperative variables that make it difficult to compare data, and highly variable complication rates.

Tongue-Lip Adhesion

Tongue-lip adhesion continues to be an effective surgical modality in the treatment of some infants with TBAO based on level 4 or 5 data. Twenty studies included TLA as a surgical intervention, all level 4 or 5 studies. Successful management of the airway using this technique ranged from 71% to 100% in the case series identified; however, the larger series published rates closer to 70%.[13,55-58] Its widespread acceptance has been limited, however, by postoperative complications, the need for further secondary procedures, and a lack of comparative, cohort-controlled studies with other available treatment modalities. Flap dehiscence persists as a problem, despite modifications from the original Douglas technique,[59] with reports ranging from 0% to 57%.[‡] Most studies, however, report rates between 20% and 30%. Although Denny et al[56] cite an initial success rate of 82% using TLA, 91% underwent secondary surgery, with 54% requiring G-tube placement for supplemental nutrition and 27% requiring mandibular distraction for airway control. The rate of secondary procedures (35%) was lower in the case series by Huang et al,[58] with 21% requiring tracheostomy after TLA. Only 1 of the 20 included studies reported outcomes based on data from a uniform patient population.[60] Most studies reported their data with a mixed population, making determination of outcomes more difficult.

Other Surgical Modalities for Intervention

In addition to the most commonly cited techniques of MD and TLA, mandibular traction,[34] transmandibular K-wire,[29,61] and subperiosteal release[28,40,62-64] have also been described in the literature for the treatment of TBAO. Of the 8 studies describing these other modalities, all are level 4 and 5 studies. Pradel et al[34] used mandibular traction on infants who failed other conservative measures and was able to extubate all children after 2 to 11 days. Of the 2 reports on the use of transmandibular K-wire, the first study[59] reported no benefit even in conjunction with a TLA, and the second report[22] suggested a 100% success in conjunction with the use of a nasopharyngeal (NP) airway. Of the studies evaluating the efficacy of subperiosteal release, only 3 presented treatment-specific outcomes.[40,63,64] In these 3 studies, the need for a tracheostomy after subperiosteal release ranged from 10% to 100%.[40,63,64] Of these studies, 1 reported a complication rate of 10% due to wound infection.[40]

Outcomes

Morbidity and Mortality. Significant morbidity and mortality have been described with neonatal TBAO. The most significant morbidities described in association with severe persistent TBAO are cor pulmonale and congestive heart failure, which have been shown to occur in as many as 10% to 30% of infants.[65-67] Recent case studies no longer describe associated cor pulmonale, however, likely because of better recognition of airway obstruction and its consequences. In contrast, overall mortality rates for patients with TBAO have shown little change over the past 30 years despite new therapies. Twenty-four studies were reviewed that document mortality in children with TBAO. Death still occurs with upper airway obstruction, with documented mortality for all patients ranging from 0% to 21% (median 4.5%).[§] Caouette-Laberge et al[40] provided mortality data demonstrating that infants with syndromic upper airway obstruction or associated anomalies had a significantly higher rate of mortality when compared with isolated upper airway obstruction (22.8% vs 5.9%), as did premature infants when compared with term infants with upper airway obstruction (60.0% vs 9.5%). This may explain the low but persistent mortality associated with neonatal TBAO. The existing mortality data are difficult to interpret, however, as most reports are based on case series of infants with a mix of mild to severe airway obstruction, receiving multiple interventions. Contributing factors, such as syndromes and prematurity, are not defined, and reported mortality rates are limited to hospital discharge in some reports, whereas others report mortality based on long-term follow-up.

Polysomnography Outcomes. Fifteen studies were found that used PSG in neonates with TBAO to document the presence and severity of obstructive breathing during sleep and to measure outcomes after surgical intervention.[‖] Three studies used PSG in patients before and after TLA and suggested improvement in postoperative PSG, but quantitative data were not provided.[39,55,57] Cohen et al[71] used PSG after a variety of surgical interventions and showed that the average RDI improved from severe to mild, and the average oxygen saturation nadir rose from 61% to 92%. A crossover study by Buchenau et al[25] found a decrease in the apnea index (AI) in neonates treated with a preepiglottic baton plate but no change with a conventional palatal plate. Studies have reported improvement in measures of obstructive sleep apnea after MD, but many do not provide detailed data.[41,45-48] More specific PSG data were provided in a few studies that demonstrate that RDI, or a comparable index, decreased from severe to normal or mild after MD.[42,49-51,75] Interpretation of the available studies using PSG as an outcome measure after surgical intervention in neonates with TBAO is problematic, as they often lack details

[†]References 27, 33, 41, 42, 45, 49, 50, 53.
[‡]References 11, 13, 14, 17, 20, 30, 55-58.
[§]References 12, 15, 17, 30, 34, 40, 50, 55, 63, 68-74.
[‖]References 25, 39, 41, 42, 45-51, 57, 71, 75, 76.

regarding the performance and scoring of PSGs and do not report complete PSG data, hindering interpretation and replication of these results. A more thorough understanding and reporting of PSG data by managing clinicians is necessary for quantitative comparison between centers.

Feeding. Forty-eight studies of infants with neonatal TBAO or PRS were reviewed for feeding outcomes. The studies address the effect of specific airway interventions on feeding and feeding equipment modifications. They demonstrate a higher prevalence of oral motor dysfunction in the presence of obstruction and decreased oral feeding success for syndromic patients.[5,77-79] Two retrospective case series evaluated the use of a palatal obturator to correct feeding problems and noted no significant improvement.[12,14] However, both studies used multiple airway interventions and had mixed populations of isolated and syndromic infants, which limited evaluation. Four retrospective case series focused on the feeding outcomes of syndromic infants vs those with isolated airway obstruction and found that those with syndromes were more likely to require nonoral feeding interventions.[5,77-79] Many studies have documented the effect of specific airway interventions on feeding success. These studies document short-term feeding outcomes within 4 weeks or less of intervention.[¶] A comparison of these studies showed that infants treated with prone positioning or MD as their airway intervention were more successful at achieving total oral feeding within 1 month posttreatment. However, analysis of the data is limited as there is no definition of obstructive severity and no standard means of documenting successful airway intervention, no defined means used to document achievement of oral feeds, no objective documentation that infants met their nutritional needs, and no standard timeframe for reevaluation. Five case series evaluated the incidence of reflux in infants with upper airway obstruction. Using esophageal pH probes, 2 studies compared the incidence of reflux in children with PRS to normal controls and documented increased reflux in PRS until at least 2 months of age.[72,80] Finally, no randomized controlled trials exist to evaluate the effectiveness of clinical interventions for reflux in neonates with TBAO.

Growth. Eleven case series were reviewed that used standardized growth measurements, percentile ranking, and/or growth velocity to compare growth of infants with upper airway obstruction.[#] The likelihood of achieving normal growth was highest in infants with isolated upper airway obstruction and in those receiving feeding assistance by nasogastric tube when oral intake was inadequate. Infants with syndromes started with lower than normal height and weight and continued to have delayed growth over time. The use of a hypercaloric diet was evaluated in 1 case-control series, demonstrating that infants receiving the diet did not meet growth standards without nasogastric feeding supplementation.[83]

Length of Stay. Thirteen studies were reviewed that documented average length of stay for patients with TBAO. Length of stay varied significantly with treatment type and the year of study.[**] Early studies, where treatment with prone positioning or NP tubes occurred primarily in the hospital, document prolonged lengths of stay of 30 to 60 days. More recent studies document shorter stays of 10 to 20 days for patients treated with NP tubes, primarily due to educational programs and home health programs designed to allow home management.[82,87] The more recent use of MD has also resulted in an equivalent shorter stay of 12 to 18 days during the first hospitalization, but the length of stay reported does not reflect the consolidation phase and later return for device removal.[34,41,48] Thus, although recent trends show a shorter length of stay, length of stay does not equate to length of care, and although initial hospital stays have been decreased to 2 to 3 weeks, home care may remain intensive for weeks to months. The time, effort, and vigilance required to care for children with NP tubes, MD devices, and nasogastric feeds at home are not documented in the literature.

Hearing and Speech Outcomes. Few studies have evaluated the effects of neonatal TBAO on hearing and speech. Two published studies documented speech outcomes and 3 studies documented hearing outcomes for PRS patients. Lehman et al[86] found that 65.4% of PRS patients had normal or good speech, including good intelligibility, no nasal emission, and normal resonance. LeBlanc and Golding-Kushner[89] evaluated PRS patients who were treated with TLA and compared their speech to cleft palate patients matched for syndrome. They found a 2- to 4-month delay in speech following tongue release and palatoplasty for PRS patients, but this difference could no longer be detected at 12 months. Evaluations of hearing have shown that patients with PRS have a high rate of conductive hearing loss (60%-83%) and a high rate of middle ear effusion requiring myringotomy tubes (63%-64%).[14,84,90] Hearing loss in PRS patients occurs more frequently in syndromic PRS patients and is usually bilateral and conductive, with only 1 case of sensorineural hearing loss identified in 43 described patients.[84,90]

Neurodevelopment. Very few studies have evaluated developmental delay or school outcomes for children with TBAO. Six studies were evaluated that report on neurodevelopmental impairment (NDI). When cohorts of PRS patients have been evaluated, rates of NDI range from 11.5% to 23.8%.[15,18,39,66,91,92] Similar to the studies on mortality, several authors have shown that rates of NDI are significantly higher in children with syndromes or associated abnormalities (23%-66%) when compared with nonsyndromic patients (7.6%-10%) and are higher than the general population.[15,18,39] Drescher et al[92] showed that infants with isolated upper airway obstruction had cognitive development that fell within the normal reference range, but PRS patients consistently demonstrated worse cognitive development than controls in sequential processing ($P = .003$),

[¶]References 5, 30, 35, 41, 44, 46, 48, 60, 68, 70, 73, 77.
[#]References 13, 15, 20, 22, 35, 73, 81-85.
[**]References 20, 29, 30, 34, 35, 41, 48, 80, 82, 83, 86-88.

simultaneous processing (P = .002), mental processing (P = .001), and achievement scores (P = .005). No difference was found in psychosocial development.

Discussion

Development of a standardized treatment algorithm for neonates with TBAO is hindered by several shortcomings in the current literature, making a side-by-side comparison of treatment options difficult. Guidelines or indications for intervention, whether conservative or surgical, are vaguely outlined or not described in the published literature. This problem arises because there is no standardization in making the diagnosis as detailed above, as well as no consensus on the indications for intervention in this patient population. Reported indications vary from jaw index <5% and evidence of aerodigestive tract obstruction[93]; oxygen saturation in prone position of less than 40%[93]; hypercapnia, acidosis, and desaturations to <85%[34]; oxygen saturation of <90% or no weight gain within 15 days of birth; and apnea, lack of appropriate weigh gain, or lack of parental compliance.[42] The lack of a consensus for intervention in neonates with TBAO arises mostly from a lack of direct comparison of conservatively managed disease to surgically managed disease.

The second limitation is that there is no uniformity in cohort description and selection within each study itself or from one study to another. Most studies include a heterogeneous cohort composed of children with isolated TBAO, those associated with a defined syndrome, and unique PRS. Therefore, the conclusion reported by Smith and Senders[5] in which airway intervention beyond position therapy was required in 28% of patients with isolated PRS, 42% of patients with PRS plus a defined syndrome, and 58% of patients with unique PRS is typical of the current literature. Although these studies prove that medically complex children in general are more likely to require surgical intervention, the nonuniformity of the cohorts makes it difficult to apply these studies to the development of a treatment plan for a specific TBAO phenotype.

The third limitation of the current literature is the variability of surgical technique between studies. For example, different studies have described different surgical end points for MD ranging from 12 to 17 mm.[94-97] Many variables involved in performing distraction (device selection, method and location of performing the mandibular osteotomy or corticotomy, length of the latency phase, rate and rhythm of distraction phase, length and end point of consolidation phase, and methods of analyzing clinical progress) make comparing distraction patients difficult. Similar arguments can be made for some of the other conservative and surgical interventions, given that there is no standardization of the intervention among different centers.

Finally, the fourth limitation of the current studies is the lack of standardization of reporting outcomes after conservative or surgical intervention for TBAO. This limitation, as the first limitation described above, arises from a lack of understanding the physiological consequences. Because TBAO leads to a compromised airway, it is generally agreed that the most direct physiological consequences are labored breathing, especially during sleep, dysphagia, and poor weight gain. However, different investigators have chosen to report different measures, making a side-by-side comparison of treatment efficacy difficult.

There is sparse high-level evidence in the published literature to aid the clinician in the care of the neonate with upper airway obstruction. This systematic review shows that the literature provides little more than single-center case studies with insufficient information regarding patient characteristics and standards for treatment decision. Before there is an agreed-upon method for diagnosis and a clear role for any treatment modality for patients with significant upper airway obstruction, carefully designed prospective studies must be conducted. These studies should incorporate standardized patient selection, preoperative evaluation methods to allow for objective assessment and reporting, and short- and long-term outcome measures based on uniform standards.[98] In addition, the use of a defined protocol for feeding intervention, with documentation of feeding and growth parameters, will allow objective evaluation and comparison of patient growth among the various treatment modalities. We acknowledge the inherent heterogeneity within the patient population and the associated challenges surrounding studying design. However, we would recommend objective measures of evaluation such as preoperative documentation of cephalometrics, TBAO documented on cephalogram, endoscopy, or 3-dimensional computed tomography (CT) as well as growth documentation compared with norms, need for feeding assistance, and secondary surgeries, and long-term hearing, speech, and neurodevelopmental outcomes.

Strengths and Limitations of the Review

This review assesses the best evidence available, at the time of publication, for the diagnosis, treatment, and long-term outcomes of neonates with TBAO. The strength of this review is that an extensive literature search in relevant databases reviewing 30 years of relevant studies was performed, and each study was reviewed by 2 independent readers to ensure accuracy of data. However, this review has several limitations. Non-English-language articles were excluded, but we feel that this has not had any major impact on our findings as there are no published randomized controlled trials with the defined patient population. The quality of the case series varied, with poor and inconsistent reporting of population characteristics. This limited any further subgroup analysis or stratification by risk factors and made it difficult to make recommendations based on available data.

Conclusions

A comprehensive systematic review of the literature regarding the level of evidence for the diagnosis, treatment, and long-term outcomes of neonates with TBAO has led to several determinations. (1) It is difficult to extrapolate from literature because of the variability between studies in cohort phenotype; (2) treatment

outcomes are difficult to compare between studies because of the variability of inclusion and exclusion criteria, as well as the lack of standardized indications for intervention; and (3) long-term outcomes of the various treatment modalities are difficult to describe because of the paucity of data.

To make progress in understanding TBAO, as well as develop the tools necessary to expeditiously diagnose TBAO and efficacious treatment modalities, the following measures have to be taken. Multiple centers dedicated to the treatment of these patients must join together in their research endeavors to achieve cohort sizes that allow statistical analysis, given the relative paucity of patients with PRS and TBAO. Standardized criteria and nomenclature must be developed for identifying and describing patients with TBAO. Indications for surgical treatment have to be standardized and clearly described in studies. Outcome measures have to be standardized and adequately measured in both the short and long term. In the absence of sufficient evidence to develop standardized algorithms for the diagnosis and treatment of infants with TBAO, expert panels can be organized to develop protocols. These protocols can then be validated in a prospective manner.

Author Contributions

Laurel B. Bookman, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Kristin R. Melton**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Brian S. Pan**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Patricia L. Bender**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Barbara A. Chini**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **James M. Greenberg**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Howard M. Saal**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Jesse A. Taylor**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript; **Ravindhra G. Elluru**, study conception and design, analysis/interpretation of data, drafting and critical revision of article, final approval of manuscript.

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Supplemental Material

Additional supporting information may be found at http://oto.sagepub.com/content/by/supplemental-data

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††Citations to references 99 to 126 are included in the online appendix.

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