

REVIEW

Tracheal anomalies associated with Down syndrome: A systematic review

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Abstract

Introduction: Airway anomalies are accountable for a substantial part of morbidity and mortality in children with Down syndrome (DS). Although tracheal anomalies occur more often in DS children, a structured overview on the topic is lacking. We systematically reviewed the characteristics of tracheal anomalies in DS children.

Methods: A MEDLINE and EMBASE search for DS and tracheal anomalies was performed. Tracheal anomalies included tracheal stenosis, complete tracheal ring deformity (CTRD), tracheal bronchus, tracheomalacia, tracheal web, tracheal agenesis or atresia, laryngotracheoesophageal cleft type 3 or 4, trachea sleeve, and absent tracheal rings.

Results: Fifty-nine articles were included. The trachea of DS children is significantly smaller than non-DS children. Tracheomalacia and tracheal bronchus are seen significantly more often in DS children. Furthermore, tracheal stenosis, CTRD, and tracheal compression by vascular structures are seen regularly in children with DS. These findings are reflected by the significantly higher frequency of tracheostomy and tracheoplasty performed in DS children.

Conclusion: In children with DS, tracheal anomalies occur more frequently and tracheal surgery is performed more frequently than in non-DS children. When complaints indicative of tracheal airway obstruction like biphasic stridor, dyspnea, or wheezing are present in children with DS, diagnostic rigid laryngotracheobronchoscopy with special attention to the trachea is indicated. Furthermore, imaging studies (computed tomography, magnetic resonance imaging, and ultrasound) play an important role in the workup of DS children with airway symptoms. Management depends on the type, number, and extent of tracheal anomalies. Surgical treatment seems to be the mainstay in severe cases.

KEYWORDS

complete tracheal ring deformity, Down syndrome, tracheal bronchus, tracheal disorders, tracheomalacia

1 | INTRODUCTION

Down syndrome (DS) or trisomy 21 is the most prevalent chromosomal disorder in humans, affecting approximately 1 in 625 live births.¹ DS causes a broad spectrum of anatomical variations in the head and neck area, warranting otorhinolaryngological consultation in approximately 50% of children with DS.^{2,3} Airway anomalies are accountable for a substantial part of morbidity and mortality in children with DS.^{4,5} Upper airway anomalies in DS children are well-described in literature and well-known to physicians treating DS children with airway symptoms.⁶ Little attention is directed toward tracheal anomalies.

In the general pediatric population, tracheal anomalies are relatively uncommon and no incidence for the spectrum of tracheal anomalies is described in the literature. Presenting symptoms may include stridor, dyspnea, cough, recurrent respiratory infections or cyanosis. However, some anomalies like tracheal bronchus can remain asymptomatic and are incidental findings on imaging. Diagnosis of tracheal anomalies is primarily established by rigid endoscopic tracheobronchoscopy, as both structural disorders like tracheal stenosis or complete tracheal ring deformity (CTRD) as well as functional disorders like tracheomalacia or tracheal compression by vascular structures can be identified. As tracheobronchoscopy is only performed in symptomatic patients, tracheal anomalies are considered to occur more frequently than reported. Furthermore, tracheal anomalies often coincide with congenital disorders other than airway or respiratory anomalies, including congenital heart disease, vascular anomalies, or gastrointestinal defects.⁷

Although tracheal anomalies are rare, they occur more often in DS children than in non-DS children.⁸ A structured overview of the prevalence and treatment options of tracheal anomalies in DS children is missing in the literature. The aim of this systematic review is to describe these characteristics of tracheal anomalies in DS children and to create awareness for tracheal anomalies among clinicians treating DS children with respiratory complaints.

2 | MATERIALS AND METHODS

This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹ We sought to review all original studies (case study, case-control study, cohort study, controlled clinical trial, or randomized controlled trial) on tracheal anomalies in children with DS and present the results in a narrative fashion. Tracheal anomalies eligible for assessment included congenital and acquired tracheal stenosis, CTRD, tracheal bronchus (also known as “pig bronchus” or “bronchus suis”), tracheal compression by vascular structures, tracheomalacia (with or without bronchomalacia), tracheal web, tracheal agenesis or atresia, laryngotracheoesophageal cleft type 3 or 4, trachea sleeve or absent tracheal rings. Exclusion criteria were studies without DS patients, patients aged >18 years old, or airway anomalies not related to the trachea (for instance sleep apnea, subglottic stenosis, laryngomalacia,

laryngeal cleft grade 1 or 2, vocal cord paralysis, or infectious diseases).

A medical information specialist (J. L.) performed a broad search in OVID MEDLINE and OVID EMBASE from inception to November 16, 2020 using controlled terms (i.e., MeSH-terms) and text words for DS and tracheal anomalies (see Supporting Information Appendix A). No language, date, or other restrictions were applied. Conference abstracts were excluded from EMBASE. The records retrieved were imported and de-duplicated in EndNote X9. Two authors (M. M. F. and M. H.) independently screened all records on title and abstract using the web application Rayyan (rayyan.qcri.org). If the study potentially met inclusion criteria, the full text was obtained and assessed for inclusion eligibility. Any disagreements were reviewed and discussed with a third author (F. G. D.) until consensus.

To improve readability for clinicians confronted with DS children with tracheal anomalies, included articles are presented in a narrative fashion for each individual tracheal disorder.

3 | RESULTS

The search retrieved 748 unique publications, which were screened on title and abstract (see flowchart in Figure 1). Of the 135 full-text publications assessed, 59 articles met inclusion criteria. The prevalence of each individual tracheal anomaly is presented in Table 1.

3.1 | Congenital and acquired tracheal stenosis

Nine articles on congenital and acquired tracheal stenosis in DS children were included.^{10–18}

A narrowed trachea is considered a congenital feature of DS. In a prospective study on DS children without respiratory symptoms, magnetic resonance imaging (MRI) of the trachea showed a tracheal diameter 1.3–3.2 mm smaller compared with non-DS children.¹⁰

In a retrospective cohort study of DS children with airway complaints requiring diagnostic laryngotracheoscopy, congenital tracheal stenosis accounted for 5% of children.¹¹ The prevalence of symptomatic congenital tracheal stenosis in DS is estimated at 0.4%.¹¹ If a tracheal stenosis is an incidental finding or respiratory complaints are mild, no treatment is necessary. In cases of severe congenital tracheal stenosis, surgical management is indicated. In reviewed case reports on congenital tracheal stenosis in DS children, a slide tracheoplasty is performed to treat severe tracheal stenosis.^{12–14} Unfortunately, slide tracheoplasty demonstrated a poorer quality of life in children with noncardiac congenital comorbidities like DS when compared to children with isolated stenosis or healthy controls.¹⁵ Notably, all reviewed cases suffered from congenital heart disease like atrial or ventricular septal defects, confirming the association between congenital tracheal stenosis and congenital heart disease. Simultaneous repair of relatively simple congenital cardiac disease is advocated; however, complex cardiac defects are associated with an increased mortality rate.¹⁹ Interestingly, a recent study demonstrated that children with

congenital tracheal stenosis have longer trachea than controls.¹⁶ Therefore, slide tracheoplasty is considered to treat the stenosis and restore normal tracheal length.¹⁶

The prevalence of acquired tracheal stenosis is estimated at 0.8% of children with DS, as determined in a study of a complete birth cohort of DS children in the greater Glasgow (Scotland) area.¹⁷ In the studied population, acquired tracheal stenosis accounted for 6% of children with laryngotracheal airway pathology. Acquired tracheal stenosis is generally caused by intubation with an oversized tube or prolonged intubation.¹⁸ Selecting an appropriately sized endotracheal tube is, therefore, important. The proper size for endotracheal tube intubation in children with DS is considered to be 0.5–1.5 mm smaller compared with non-DS children.¹⁰ Choosing the appropriate endotracheal tube size can be helped by the air leak test, in which the ventilator pressure is slowly increased until an air leak is audible. An air leak audible between 10 and 30 cmH₂O pressure corresponds with an appropriate endotracheal tube size. Selecting the “proper size” has shown to decrease the risk of post-intubation inspiratory stridor.²⁰ Consequently, endotracheal tube size for DS children should, therefore, always be smaller than non-DS children.

3.2 | CTRD

CTRD is considered to be the most common cause of congenital tracheal stenosis in children. Our systematic review revealed 21 articles describing CTRD in children with DS.^{21–41}

Complete tracheal rings consist of “hourglass” or O-shaped cartilage rings lacking a posterior membranous part, causing stenosis of the trachea. The stenosis is frequently observed in the middle or distal part

of the trachea and may range from a few centimeters to the entire trachea.^{21–25} In 1992, the relationship between DS and CTRD was recognized in a case series of nine DS children.²⁶ The onset and course of respiratory symptoms can be highly variable. CTRD may present directly after birth or in early infancy with symptoms like stridor, wheezing, “wet” respiration, exertional dyspnea, respiratory distress, and ultimately cyanosis.²⁷ However, some children only experience respiratory symptoms during upper respiratory tract infections or after endotracheal intubation.^{28,29} Furthermore, in asymptomatic children CTRD can be discovered when advancing an endotracheal intubation tube for an elective procedure is difficult.^{22,30} The anomaly can, therefore, stay unnoticed for years, or even never be discovered at all. CTRD is generally diagnosed with rigid laryngotracheoscopy, but dynamic computed tomography (CT) can contribute if the diagnosis is doubted after laryngotracheoscopy.²⁹ In case of miscarriage in DS, CTRD can be diagnosed with microfocus CT as an addition to or replacement of postmortem examination.³¹

CTRD is associated with congenital heart disease like atrial/ventricular septal defect,^{24,32,33} tetralogy of Fallot,³⁴ persistent ductus arteriosus,³⁵ or aberrant right subclavian artery.^{21,23,36} Furthermore, congenital malformations like tracheal bronchus²¹ and complete agenesis of one lung²⁸ have been described in DS children with CTRD.

Management of CTRD depends on the severity of symptoms. In mild-to-moderate CTRD, conservative management is justified as airway growth may resolve symptoms and refrain children from surgery.⁴² In severe CTRD, surgical repair should be performed either with tracheal resection with an end-to-end anastomosis²⁵ or slide tracheoplasty.^{37,38} Tracheoplasty is performed significantly more often in children with DS than in non-DS children.³⁹ An

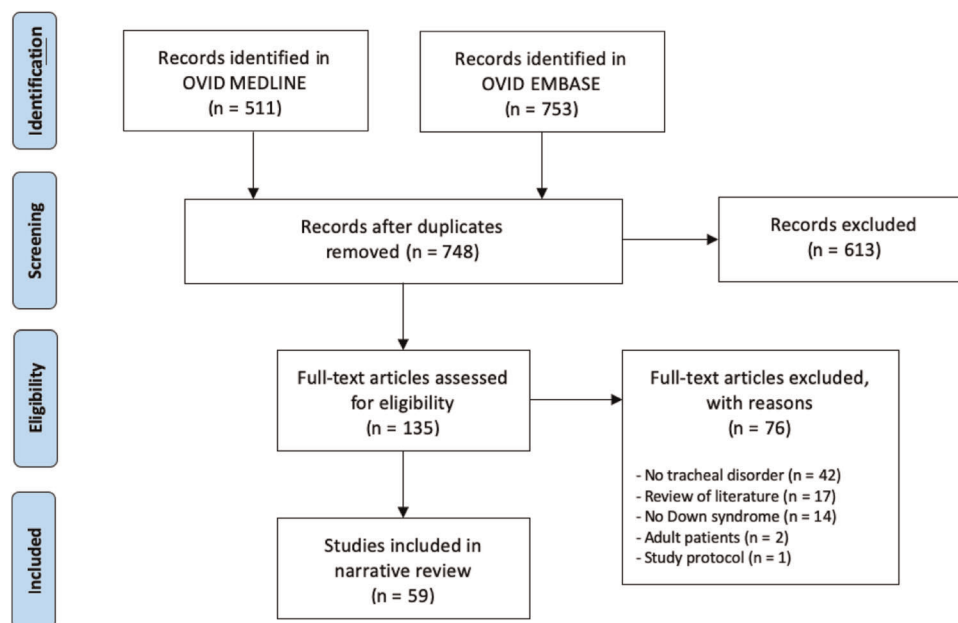


FIGURE 1 Flowchart of the study selection process for tracheal anomalies in Down syndrome [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Reported prevalence of tracheal anomalies in DS and general population

	DS (%)	DS with airway complaints and/or tracheobronchoscopy (%)	General population (%)	General population with airway complaints and/or tracheobronchoscopy (%)
Congenital tracheal stenosis	0.4	2.8–5	0.002	-
Acquired tracheal stenosis	0.8	6	-	-
Complete tracheal ring deformity	-	4	-	1.2
Tracheal bronchus	-	3.1–21	0.1–1.1	1.3–2.1
Aberrant right subclavian artery	17–28.3	6	3.3	-
Tracheomalacia	4.4–7.1	23.1–51.5	-	7.4–12.7
Tracheal web	-	4	-	0.6

Abbreviations: DS, Down syndrome; -, not reported.

interesting follow-up study on surgically treated patients showed that repaired complete tracheal rings continue to grow after slide tracheoplasty.³⁸ In asymptomatic DS children, surgical correction is not necessary. As it was demonstrated that airway lumen grows with age in children with CTRD, expectant nonsurgical management is advisable in DS children with mild respiratory complaints and a relatively short segment of complete rings.⁴⁰ Although surgical repair of CTRD often leads to a patent tracheal lumen, extensive comorbidity in children with DS may worsen survival.^{22,41}

3.3 | Tracheal bronchus

Eight articles on tracheal bronchus in DS were included in this systematic review.^{21,41,43–48}

A tracheal bronchus, also known as pig bronchus or “bronchus suis,” is defined as an anatomical variation in which an aberrant or additional bronchus originates from the supracarinal trachea. It is predominantly seen on the right side and has an estimated incidence of 0.06%–1.06%.⁴⁶ A tracheal bronchus is often asymptomatic and, therefore, reported prevalence rates in literature might underestimate the exact prevalence. However, some patients with a tracheal bronchus suffer from recurrent right upper lobe pneumonia, chronic atelectasis, or bronchiectasis.

Tracheal bronchus in DS children was first described by McLaughlin et al.⁴⁵ in 1985, who presented one DS child with recurrent pneumonia due to a right displaced apical bronchus originating from the trachea. Since then, several additional cases have been described.^{21,43,44,47,48} Interestingly, in a cohort study on children with respiratory complaints requiring flexible laryngotracheobronchoscopy, tracheal bronchus was seen in 21% of DS children compared with 2.1% in non-DS controls.⁴¹ Furthermore, a recent multicenter study on tracheal bronchus showed that 11/113 (8.3%) children with tracheal bronchus had DS.⁴⁶ As far as the affected side is described, all but one article on tracheal bronchus in DS concerned right-sided tracheal bronchus. Only Hansen et al.²¹ described a bilateral tracheal bronchus.

3.4 | Tracheal compression by vascular structures

Twenty-five articles on vascular structures causing tracheal compression were included.^{17,21,23,36,43,49–68}

Congenital heart disease is relatively common in DS as it is seen 40% of DS children.⁶⁹ Congenital vascular anomalies of the aorta and great vessels can lead to compression of the trachea and esophagus, known as a vascular ring or sling.^{23,50,66} Types of vascular structures causing tracheal compression reported in DS children include pulmonary artery sling,^{49,54,58,59} double aortic arch,^{23,56} right aortic arch with anomalous left subclavian artery,^{52,60} innominate artery,⁶¹ and aberrant right subclavian artery.^{21,23,36} One case of iatrogenic tracheal compression by a vascular structure in a DS child was identified, in which failed cardiac catheterization caused an

aneurysm of an anomalous right subclavian artery to compress the trachea.⁶⁴

Both severity of symptoms and age at presentation vary among the forms of vascular anomalies, depending predominantly on the proportion of encasement of the trachea. Rarely, compression of one main bronchus can also lead to respiratory symptoms.⁴³ Presenting symptoms include stridor, wheezing, dyspnea, cyanosis, and eventually respiratory distress. Associated feeding problems should raise suspicion for the presence of a vascular sling causing concomitant esophageal compression. Fetal endosonography enables prenatal diagnosis of vascular anomalies like aberrant right subclavian artery, double aortic arch, and right aortic arch with anomalous left subclavian artery in children with DS.^{62,63,65,67,68} Interestingly, an aberrant right subclavian artery is considered an indicator for chromosomal abnormalities as it is seen in 17%–28.3% of DS fetuses.^{51,53,57} On the contrary, symptomatic vascular compression of the trachea and esophagus is very rare. A cohort study of DS children showed an aberrant right subclavian artery in only 6% of children undergoing tracheobronchoscopy.¹⁷ Vascular compression of the trachea is managed conservatively or with surgical correction. Surgical procedures include division of the vascular malformation and/or tracheal cartilage framework surgery, depending on the type of vascular malformation and the location and extent of tracheal compression.^{23,55}

Interestingly, vascular tracheal compression is associated with CTRD. In DS children, we identified three cases of DS children suffering airway obstruction due to an aberrant right subclavian artery and CTRD.^{21,23,36} To our knowledge, there is no embryologic explanation for this association.

3.5 | Tracheomalacia

Nine articles on tracheomalacia in DS children were included.^{11,14,17,41,43,44,70–72}

Tracheomalacia is characterized by the collapse of the tracheal lumen on expiration attributed to cartilage weakness. Airway collapse can also involve both the trachea and the bronchi (tracheobronchomalacia), or just the bronchi (bronchomalacia). When no specification on the site of collapse is given; the general term airway malacia is used to describe airway collapse of trachea, bronchi, or both. Tracheomalacia can occur independently, but is also associated with tracheoesophageal fistula, tracheal compression by a vascular ring, or congenital heart disease. Presenting symptoms include stridor, dyspnea at rest or on exertion, wheezing, barking cough, cyanosis, or recurrent pneumonia.

In cohort studies on DS children, the prevalence of airway malacia ranges from 4.4% to 7.1%.^{11,17} In DS children requiring endoscopic evaluation of the airway because of respiratory complaints, airway malacia was observed in 32.4%–46%.^{11,41,44} When compared with non-DS controls with airway complaints, airway malacia was observed significantly more often (33% in DS vs. 7.4% in controls). Furthermore, associated morbidities in DS children with airway malacia include congenital heart disease and pulmonary arterial hypertension.^{43,70,72} Although the severity of symptoms may differ among DS children,

pediatric intensive care unit admission may be necessary.⁷¹ Treatment for tracheobronchomalacia depends on the severity of symptoms: whereas children with mild-to-moderate tracheobronchomalacia may be effectively treated with medication (corticosteroids/ipratropium bromide inhalers, saline nebulizers, and/or intermittent courses of antibiotics) or supportive treatment (oxygen supply, high flow nasal canula, or nasal continuous positive airway pressure), children with severe tracheobronchomalacia require a surgical intervention. Surgical options to improve the tracheal lumen include anterior aortopexy, in which the aorta is pulled anteriorly toward the sternum, and posterior tracheopexy, in which the trachea is attached to the anterior longitudinal ligament of the spine.⁶⁷ Furthermore, stenting the airway with an internal stent is potentially a promising concept but currently reserved for patients who have no curative surgical options or as an alternative for tracheostomy, as stents generally lead to a wide range of problems like mucus plugging, granulation tissue/crust formation, stent migration, or difficulty/inability to remove the stent.^{14,72}

3.6 | Tracheal web

A tracheal web is a thin layer of tissue that narrows the tracheal lumen, but never fully occludes the trachea. It can either be congenital or acquired as a result of intubation. Only one report described a DS child with a tracheal web, covering 30% of the tracheal lumen.⁴¹ No surgical intervention was necessary. In the non-DS population in that study, two children with tracheal web were found, resulting in an overall prevalence of 0.6%.

3.7 | Tracheal agenesis and atresia

The absence of the trachea (agenesis) or partial underdevelopment of the trachea (atresia) is a very rare congenital disorder. The condition is generally associated with rapid postnatal death. In cases of proximal tracheal atresia in which in utero ultrasound confirms the diagnosis, survival through an ex utero intrapartum treatment procedure may be accomplished.^{73,74} In our systematic review, no association between tracheal agenesis or atresia and DS is described.

3.8 | Other tracheal anomalies

Our systematic search showed no literature on DS children with tracheal anomalies such as laryngotracheoesophageal cleft (Grade 3 or 4), tracheal cartilaginous sleeve, or absent tracheal rings.

3.9 | Multiple synchronous tracheal anomalies

Prevalence of multiple synchronous tracheal anomalies is very rare, as we identified only four DS children with more than one tracheal

anomaly. Devine et al.³⁶ reported a DS neonate with respiratory insufficiency due to both a narrow trachea with 15 complete tracheal rings and an aberrant right subclavian artery. The association between CTRD and aberrant right subclavian artery in DS children was confirmed in two additional cases.^{21,23} Furthermore, our review identified a case of a DS neonate with airway complaints due to a congenital tracheal stenosis and tracheomalacia.¹⁴

4 | DISCUSSION

This systematic review comprehensively discusses the range of tracheal anomalies that occur in children with DS. The prevalence of tracheal anomalies like tracheomalacia and tracheal bronchus is significantly higher in children with DS.⁴¹ Furthermore, tracheal anomalies like congenital and acquired tracheal stenosis, CTRD, tracheal compression by vascular structures, and tracheal web have been well documented in children with DS. These findings are reflected by the significantly higher frequency of tracheostomy and tracheoplasty performed in DS children when compared with non-DS children.³⁹

Although this systematic review focuses on tracheal anomalies, it is important to recognize that respiratory symptoms in DS children are often multifactorial and can be attributed to both the respiratory system as well as other organ systems. Children with DS are more susceptible to respiratory tract infections and lung injury due to parenchymal abnormalities like reduced alveolar surface area and reduced ciliary beat frequency and movement.⁸ The characteristic anatomical abnormalities of the upper airway and hypotonia associated with DS are accountable for the high prevalence of obstructive sleep apnea in DS children (50%–97%, compared with 1%–2% in non-DS children).⁸ Furthermore, respiratory symptoms in children with DS may be maintained or worsened by congenital heart disease and its associated surgical complications, gastroesophageal reflux, and reduced immune system including variable T- and B-cell lymphopenia and suboptimal response to standard immunizations.⁸

To the best of our knowledge, there is no clear and straightforward embryological explanation for the association of DS and the described variety of tracheal anomalies. The embryonic development of the trachea and its cartilage is known to some extent. At around 26–30 days of development, the respiratory diverticulum is formed and subsequently grows in a caudal direction to create the tracheal lumen. Tracheal cartilage subsequently appears from mesenchymal growth centers at 51–54 days.⁷⁵

The etiology of tracheal anomalies is generally attributed to either malformed tracheal cartilage or tracheal compression by nearby vascular structures.⁷⁶ To our knowledge, only one embryological study demonstrated a relation between DS and abnormal cartilage. In this report, rib cartilage of DS fetuses of 17–22 weeks showed an abnormal growth maturation pattern when compared with non-DS fetuses.⁷⁷ This finding was, however, only found in rib cartilage and not

confirmed in femoral, vertebral, or skull cartilage. Unfortunately, no attention was directed to tracheal cartilage in this study.

The development of the aorta and great vessels is complex and providing a detailed description goes beyond the extent of this review. Development takes place from the embryonic age of 18–50 days, thus coinciding with the development of the trachea. Although the synchronous presence of disorders related to malformed tracheal cartilage (e.g., CTRD or tracheomalacia) and congenital heart and great vessel disease is widely reported, an embryological understanding of this association is lacking. In general, the pathophysiology of vascular structures causing trachea compression is attributed to the disorderly development of the aortic arches.⁷⁸ The most widespread theory, based on “hypothetical double aortic arch with bilateral patent ducti arteriosi,” was first coined in 1948 and attributed congenital vascular anomalies to failure of (a number of) aortic arches to regress.⁷⁹ This theory was strengthened in 1994 by a case report of a DS girl with bilateral patent ducti arteriosi.⁸⁰

Although our review presents a systematic overview of tracheal anomalies in DS, we reckon that publication bias plays an important role in the current knowledge of these anomalies. Many published articles concern case reports or case series, while quite a few “tracheologists” (otorhinolaryngologists regularly performing endoscopy of the pediatric trachea) will have been confronted regularly with these anomalies in DS children. However, their findings might not have been published as the prevalence of tracheal anomalies is very low.

5 | CONCLUSION

In children with DS, tracheal anomalies occur more frequently and tracheal surgery (tracheostomy and tracheoplasty) is performed more frequently than in non-DS children. A wide variety of tracheal anomalies like tracheomalacia, tracheal stenosis, tracheal bronchus, CTRD, and tracheal compression by vascular structures can be responsible for respiratory complaints in children with DS. When complaints indicative of tracheal airway obstruction like biphasic stridor, dyspnea, or wheezing are present, diagnostic rigid laryngo-tracheobronchoscopy with special attention to the trachea is indicated. Furthermore, imaging studies (CT, MRI, and ultrasound) play an important role in the workup of DS children with airway symptoms. Management depends on the type, number, and extent of tracheal anomalies. Surgical treatment seems to be the mainstay in severe cases.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

M. Matthijs Fockens: Conceptualization (lead); methodology (supporting); investigation (equal); Writing—original draft (lead); visualization (lead). **Michiel Hölscher:** Investigation (equal); Writing—review and editing (equal). **Jacqueline Limpens:** Methodology (lead); writing—review and editing (equal). **Frederik G. Dijkers:** Conceptualization (supporting); writing—review and editing (equal); supervision (lead).

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REFERENCES

- Weijerman ME, de Winter JP. Clinical practice. The care of children with Down syndrome. *Eur J Pediatr.* 2010;169(12):1445-1452.
- Chin CJ, Khami MM, Husein M. A general review of the otolaryngologic manifestations of Down Syndrome. *Int J Pediatr Otorhinolaryngol.* 2014;78(6):899-904.
- Hans PS, Belloso A, Sheehan PZ. Parental satisfaction with health services provided to children with Down syndrome in north-west England: an ENT perspective. *J Laryngol Otol.* 2007;121(4):382-386.
- Yang Q, Rasmussen SA, Friedman JM. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. *Lancet.* 2002;359(9311):1019-1025.
- So SA, Urbano RC, Hodapp RM. Hospitalizations of infants and young children with Down syndrome: evidence from inpatient person-records from a statewide administrative database. *J Intellect Disabil Res.* 2007;51(Pt 12):1030-1038.
- Watts R, Vyas H. An overview of respiratory problems in children with Down's syndrome. *Arch Dis Child.* 2013;98(10):812-817.
- Schweiger C, Cohen AP, Rutter MJ. Tracheal and bronchial stenoses and other obstructive conditions. *J Thorac Dis.* 2016;8(11):3369-3378.
- Alsubie HS, Rosen D. The evaluation and management of respiratory disease in children with Down syndrome (DS). *Paediatr Respir Rev.* 2018;26:49-54.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items For Systematic Reviews and Meta-analyses: the PRISMA statement. *PLOS Med.* 2009;6(7):e1000097.
- Shott SR. Down syndrome: analysis of airway size and a guide for appropriate intubation. *Laryngoscope.* 2000;110(4):585-592.
- Jacobs IN, Gray RF, Todd NW. Upper airway obstruction in children with Down syndrome. *Arch Otolaryngol Head Neck Surg.* 1996;122(9):945-950.
- Kan CD, Wu JM, Wu MH, Yang YJ. Tracheal stenosis associated with ventricular septal defect in a Down syndrome baby—a case report. *Acta Cardiol Sin.* 1998;14(1):46-51.
- Kelleher EM, Nolke L, McMahon CJ. Successful slide tracheoplasty and partial atrioventricular septal defect repair following extracorporeal membrane oxygenation support. *Cardiol Young.* 2015;25(3):573-575.
- Nakamura Y, Aoki M, Nagase Y, Fujiwara T. Removal of an external stent of the bronchus. *Interact Cardiovasc Thorac Surg.* 2010;10(3):457-458.
- Wray J, Ryde M, Butler CR, Hewitt RJ. Quality of life can be good after slide tracheoplasty for long-segment tracheal stenosis. *Interact Cardiovasc Thorac Surg.* 2019;29(6):876-882.
- Chen S-J, Wu E-T, Wang C-C, Chou H-W, Chen Y-S, Huang S-C. Excessive tracheal length in patients with congenital tracheal stenosis. *Ann Thorac Surg.* 2019;108(1):138-145.
- Hamilton J, Yaneza MMC, Clement WA, Kubba H. The prevalence of airway problems in children with Down's syndrome. *Int J Pediatr Otorhinolaryngol.* 2016;81:1-4.
- Sahu MK, Chalattil B, Karanjkar A, et al. Severe subglottic tracheal stenosis dictates intercontinental transfer of a 2-year-old child with tracheostomy tube in situ. *J Card Crit Care.* 2020;03(01):45-48.
- Okamoto T, Nishijima E, Maruo A, et al. Congenital tracheal stenosis: the prognostic significance of associated cardiovascular anomalies and the optimal timing of surgical treatment. *J Pediatr Surg.* 2009;44(2):325-328.
- Koka BV, Jeon IS, Andre JM, MacKay I, Smith RM. Postintubation croup in children. *Anesth Analg.* 1977;56(4):501-505.
- Hansen DD, Haber Kern CM, Jonas RA, Davis PJ, McGowan FX. Case 1—1991. Tracheal stenosis in an infant with Down's syndrome and complex congenital heart defect. *J Cardiothorac Vasc Anesth.* 1991;5(1):81-85.
- Mambrino LJ, Kenna MA, Seashore J. Surgical management of tracheal stenosis in an infant with multiple congenital anomalies: when is baby inoperable? *Ann Otol Rhinol Laryngol.* 1991;100(3):198-200.
- Phelan E, Ryan S, Rowley H. Vascular rings and slings: interesting vascular anomalies. *J Laryngol Otol.* 2011;125(11):1158-1163.
- Resheidat A, Kelly T, Mossad E. Incidental diagnosis of congenital tracheal stenosis in children with congenital heart disease presenting for cardiac surgery. *J Cardiothorac Vasc Anesth.* 2019;33(3):781-784.
- Weber TR, Fiore A. An association of congenital mid-tracheal stenosis with Down syndrome. *Surgery.* 2000;127(3):358-360.
- Wells TR, Landing BH, Shamszadeh M, Thompson JW, Bove KE, Caron KH. Association of Down syndrome and segmental tracheal stenosis with ring tracheal cartilages: a review of nine cases. *Pediatr Pathol.* 1992;12(5):673-682.
- Kylat RI. Tracheal stenosis and congenital heart disease in trisomy 21. *Children (Basel).* 2019;6(9):98.
- Bravo MNC, Kaul A, Rutter MJ, Elluru RG. Down syndrome and complete tracheal rings. *J Pediatr.* 2006;148(3):392-395.
- Swanson L, Gilley J, Masand P, Gowda S. Use of laryngeal mask airway as a bridge to extracorporeal membrane oxygenation in a neonate with undiagnosed tracheal stenosis. *Neonatal.* 2020;1(1):01.
- Farrow C, Guruswamy V. Undiagnosed tracheal stenosis in a patient with Down syndrome. *Paediatr Anaesth.* 2008;18(6):577.
- Shelmerdine SC, Ashworth MT, Calder AD, Muthialu N, Arthurs OJ. Micro-CT of tracheal stenosis in trisomy 21. *Thorax.* 2019;74(4):419-420.
- Ayoubi K, Nolke L. Use of respiratory extracorporeal life support in management of complete tracheal ring stenosis. *Ir J Med Sci.* 2012;10:S386.
- Mossad E, Resheidat A, Baker T. Incidental diagnosis of congenital tracheal stenosis in patients with congenital heart disease. *Cardiol Young.* 2017;27:S188-S189.
- Shapiro NL, Huang RY, Sangwan S, Willner A, Laks H. Tracheal stenosis and congenital heart disease in patients with Down syndrome: diagnostic approach and surgical options. *Int J Pediatr Otorhinolaryngol.* 2000;54(2-3):137-142.
- Townsend A, Mohon RT. Congenital tracheal stenosis in a patient with Down's syndrome. *Pediatr Pulmonol.* 1997;23(6):460-463.
- Devine WA, Debich DE, Taylor SR. Symmetrical bronchial pattern with normal atrial morphology. *Int J Cardiol.* 1988;20(3):395-398.
- Haughey B, Kylat R. Congenital heart disease associated trisomy 21 with complete tracheal rings. *Am J Respir Crit Care Med.* 2017;195:A4103.
- Wilcox LJ, Schweiger C, Hart CK, de Alarcon A, Peddireddy NS, Rutter MJ. Growth and management of repaired complete tracheal rings after slide tracheoplasty. *Otolaryngol Head Neck Surg.* 2019;161(1):164-170.

39. Patel TA, Nguyen SA, White DR. Down syndrome as an indicator for pediatric otolaryngologic procedures. *Int J Pediatr Otorhinolaryngol*. 2018;112:182-187.
40. Wilcox LJ, Hart CK, de Alarcon A, et al. Unrepaired complete tracheal rings: natural history and management considerations. *Otolaryngol Head Neck Surg*. 2018;158(4):729-735.
41. Bertrand P, Navarro H, Caussade S, Holmgren N, Sánchez I. Airway anomalies in children with Down syndrome: endoscopic findings. *Pediatr Pulmonol*. 2003;36(2):137-141.
42. Rutter MJ, Willging JP, Cotton RT. Nonoperative management of complete tracheal rings. *Arch Otolaryngol Head Neck Surg*. 2004;130(4):450-452.
43. Abdul-Wahab A, Janahi IA, Al-Rawi F, Mostafa OA. Diagnostic role of pediatric flexible bronchoscopy in Down's syndrome associated with congenital heart disease. *Saudi Med J*. 2006;27(9):1431-1433.
44. De Lausnay M, Verhulst S, Boel L, et al. The prevalence of lower airway anomalies in children with Down syndrome compared to controls. *Pediatr Pulmonol*. 2020;55(5):1259-1263.
45. McLaughlin FJ, Strieder DJ, Harris GB, Vawter GP, Eraklis AJ. Tracheal bronchus: association with respiratory morbidity in childhood. *J Pediatr*. 1985;106(5):751-755.
46. Moreno M, Castillo-Corullón S, Pérez-Ruiz E, et al. Spanish multi-centre study on morbidity and pathogenicity of tracheal bronchus in children. *Pediatr Pulmonol*. 2019;54(10):1610-1616.
47. O'Sullivan BP, Frassica JJ, Rayder SM. Tracheal bronchus: a cause of prolonged atelectasis in intubated children. *Chest*. 1998;113(2):537-540.
48. Pravitt J. Bronchoscopic findings in Down syndrome children with respiratory problems. *J Med Assoc Thai*. 2014;97(suppl 6):S159-S163.
49. Alsaied T, Sticka J, Unaka N, Cooper DS, Manning PB. A rare case of pulmonary artery sling and complete atrioventricular canal defect in an infant with trisomy 21. *World J Pediatr Congenit Heart Surg*. 2014;5(3):470-472.
50. Boehmer J, Berggren H, Sunnegardh J. Results after surgery for vascular rings: a study of 40 consecutive cases operated 1994-2012 in a single institution. *Cardiol Young*. 2014;24(S1):S149-S165.
51. Borenstein M, Minekawa R, Zidere V, Nicolaides KH, Allan LD. Aberrant right subclavian artery at 16 to 23 + 6 weeks of gestation: a marker for chromosomal abnormality. *Ultrasound Obstet Gynecol*. 2010;36(5):548-552.
52. Caceres J, Restrepo SM. Down syndrome and subclavian aberrant artery: a case report. *Am J Respir Crit Care Med*. 2017;195:A4101.
53. Carles D, Pelluard F, André G, Nocart N, Sauvestre F. Aberrant right subclavian artery (arteria lusoria) and the risk for trisomy 21. Retrospective study of 11,479 fetopathological examinations. *J Gynecol Obstet Biol Reprod*. 2014;43(9):698-703.
54. Conti VR, Lobe TE. Vascular sling with tracheomalacia: surgical management. *Ann Thorac Surg*. 1989;47(2):310-311.
55. Fleming WH, Umstott CE, Symbas PN, Mansour KA, Hatcher CR. The embryology and management of vascular rings. *South Med J*. 1976;69(7):878-880.
56. Gerretsen MF, Peelen W, Rammeloo LAJ, Koolbergen DR, Hrudá J. Double aortic arch with double aneuploidy—rare anomaly in combined Down and Klinefelter syndrome. *Eur J Pediatr*. 2009;168(12):1479-1481.
57. Greco E, Vigneswaran TV, Akolekar R, Zidere V, Simpson JM, Nicolaides KH. Significance and associations of aberrant right subclavian artery in the fetal cardiology setting. *Heart*. 2016;102(suppl 1):A1-A27.
58. Jayaram N, Carlson K, Swanson T, Raghuvver G. Respiratory distress secondary to a pulmonary artery sling. *J Am Coll Card*. 2015;65(suppl):A577.
59. Loureiro M, Moreira J, Vaz T, Ribeiro A, Monterroso J, Areias JC. Anomalous origin of the left pulmonary artery (Sling): a case report and review of the literature. *Rev Port Cardiol*. 1998;17(10):811-815.
60. Lugones I, Inguanzo P, Ganum G, Di Santo M, García R. Unique combination of atrioventricular septal defect with cor triatriatum and complete vascular ring. *World J Pediatr Congenit Heart Surg*. 2015;6(2):332-334.
61. McCrossan B, McCay N. Down syndrome and transposition of the great arteries. *Cardiol Young*. 2017;27(8):1630-1632.
62. Oram S, Tulloh R. Right aortic arch in fetal screening. What should we do about it? *Arch Dis Child*. 2019:A1-A279.
63. Patel CR, Lane JR, Spector ML, Smith PC. Fetal echocardiographic diagnosis of vascular rings. *J Ultrasound Med*. 2006;25(2):251-257.
64. Rodgers BM, Tabert JL, Hollenbeck JL. Aneurysm of anomalous subclavian artery: an unusual cause of dysphagia lusoria in childhood. *Ann Surg*. 1978;187(2):158-160.
65. Rosenblatt M, Pasquale J, Kurer C. Atrioventricular canal defect, pulmonary artery sling, and aortic arch anomaly in a patient with Down syndrome. *J Diagn Med Sonogr*. 2010;26(3):150-152.
66. Selman E, Sosa H, Arango Casado JE, et al. The atrioventricular canal and vascular ring. The surgical treatment of a rare anatomical association. *G Ital Cardiol*. 1994;24(5):517-519.
67. Tuo G, Volpe P, Bava GL, et al. Prenatal diagnosis and outcome of isolated vascular rings. *Am J Cardiol*. 2009;103(3):416-419.
68. Vigneswaran TV, Greco E, Simpson JM, Nicolaides KH, Zidere V. Is it important to identify an isolated right aortic arch in fetal life? *Heart*. 2016;102(suppl 1):A23.
69. Weijerman ME, van Furth AM, van der Mooren MD, et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. *Eur J Pediatr*. 2010;169(10):1195-1199.
70. Hawkins A, Langton-Hewer S, Henderson J, Tulloh RM. Management of pulmonary hypertension in Down syndrome. *Eur J Pediatr*. 2011;170(7):915-921.
71. Hilton JM, Fitzgerald DA, Cooper DM. Respiratory morbidity of hospitalized children with Trisomy 21. *J Pediatr Child Health*. 1999;35(4):383-386.
72. Lawlor C, Smithers CJ, Hamilton T, et al. Innovative management of severe tracheobronchomalacia using anterior and posterior tracheobronchopexy. *Laryngoscope*. 2020;130(2):E65-E74.
73. DeCou JM, Jones DC, Jacobs HD, Touloukian RJ. Successful ex utero intrapartum treatment (EXIT) procedure for congenital high airway obstruction syndrome (CHAOS) owing to laryngeal atresia. *J Pediatr Surg*. 1998;33(10):1563-1565.
74. Hartnick CJ, Rutter M, Lang F, Willging JP, Cotton RT. Congenital high airway obstruction syndrome and airway reconstruction: an evolving paradigm. *Arch Otolaryngol Head Neck Surg*. 2002;128(5):567-570.
75. Fockens MM, de Bakker BS, Oostra R-J, Dijkers FG. Development pattern of tracheal cartilage in human embryos [published online ahead of print September 28, 2020]. *Clin Anat*. <https://doi.org/10.1002/ca.23688>.
76. Arooj Sher Z, J Liu K. Congenital tracheal defects: embryonic development and animal models. *AIMS Genetics*. 2016;3(1):60-73.
77. Garcia-Ramírez M, Toran N, Carrascosa A, Audi L. Down's syndrome: altered chondrogenesis in fetal rib. *Pediatr Res*. 1998;44(1):93-98.
78. Kussman BD, Geva T, McGowan FX. Cardiovascular causes of airway compression. *Paediatr Anesth*. 2004;14(1):60-74.
79. Edwards JE. Anomalies of the derivatives of the aortic arch system. *Med Clin North Am*. 1948;32(4):925-949.
80. Shiralí GS, Geva T, Ott DA, Bricker JT. Double aortic arch and bilateral patent ducti arteriosi associated with transposition of the

great arteries: missing clinical link in an embryologic theory. *Am Heart J.* 1994;127(2):451-453.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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