

A 3-Month-Old Girl with a Persistent Cough and Respiratory Distress

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CASE PRESENTATION

Initial Presentation and History

A 3-month-old girl was brought to the pediatric emergency department (ED) with a nonproductive cough and difficulty breathing over the previous 2 weeks. The girl began having respiratory difficulties at 2 weeks of life, including cough, wheezing, and respiratory distress, which resulted in a diagnosis of “reactive airway disease.” Although she did not require intensive care unit admission or intubation at the time this diagnosis was made, she was admitted to the general pediatric floor and treated with steroids, levalbuterol nebulizer, and oxygen. Her symptoms improved but did not resolve, and she was discharged home on levalbuterol nebulizer treatments every 4 hours. The mother reported that over the 2 weeks prior to the current ED visit, the cough and wheezing continued with increasingly frequent post-tussive emesis despite the nebulizer treatments. The girl developed progressively decreased feeding with increased emesis and choking with meals, but there was no documented weight loss. She remained afebrile. She became increasingly fussy when laid on her back but was quickly consolable with repositioning.

The girl was born via spontaneous vaginal delivery at 39+ weeks after an uneventful pregnancy, and her initial Apgar scores were 8 at 1 minute and 9 at 5 minutes. She was discharged home with her mother on hospital day 2. She was bottle-fed and lived with her nonsmoking mother and 2-year-old brother in a carpeted apartment in the city. She did not attend day-care, but her brother had frequent play dates with neighborhood children. He had no recent illnesses. There was no family history of asthma or respiratory or cardiac disorders.

Physical Examination

Physical examination revealed a well-nourished infant in moderate respiratory distress. Vital signs were as noted in **Table 1**. Head and neck examination was normal with a notable lack of stridor, rhinorrhea, or nasal flaring. Inspection of the chest revealed supraclavicular and intercostal retractions with abdominal breathing. Auscultation of the chest revealed wheezing, bibasilar crackles, and adequate air movement. A distinct S₁ and S₂ were audible without murmur. Except for “belly breathing,” the abdominal examination was unremarkable. There was no cyanosis, clubbing, edema, or skin rash, and capillary refill time was 2 seconds.

- **What is the differential diagnosis of chronic cough in an infant?**
- **What diagnostic evaluations are indicated?**

EVALUATION OF CHRONIC COUGH

Between 7% and 10% of preschool-aged children have persistent cough symptoms daily for 3 or more weeks. In one report, 22% of preschool-aged children exhibited chronic cough without evidence of cold symptoms. It has been estimated that 50% of children younger than age 11 years raised in homes with 2 smoking parents have chronic cough symptoms.¹⁻³ Although the majority of cases can be explained by common diagnoses (including upper respiratory infections or asthma)

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Table 1. Vital Signs of the Case Patient on Admission

	Patient's Values	Normal Values for a 3-Month-Old Child
Weight (kg)	6.5	5–6
Temperature (°C [°F])	37.5 (99.5)	37 (98.6)
Pulse (bpm)	173	120–150
Blood pressure (mm Hg)	106/53	60–100/35–60
Respiratory rate (breaths/min)	32	30–50
Pulse oximetry (% on room air)	92	98–100

Table 2. Differential Diagnosis of Chronic Cough in Children

Allergic	Environmental factors
Rhinitis	Tobacco/smoke
Sinusitis	Drug abuse
Asthma	Smog
Hypersensitivity pneumonitis	House dust mites
	Animal fur/dander
Anatomic abnormalities	Fungal spores
Gastroesophageal reflux disease	Foreign body aspiration
Branchial cleft cysts	
Tracheoesophageal fistula	Psychogenic
Tracheomalacia	Psychogenic cough
Bronchiectasis	Neurologic dysfunction
Aortic arch abnormality	Laryngeal nerve dysfunction
Chronic infection	Vocal cord dysfunction
Sinusitis	Spinal nerve dysfunction
Pneumonia (viral/bacterial/fungal)	Phrenic nerve dysfunction
Recurrent bronchiolitis	Brainstem dysfunction
Recurrent laryngotracheobronchitis (croup)	
Recurrent aspiration pneumonia ± abscess	
Tuberculosis	
Pertussis	
Cystic fibrosis	
Histoplasmosis	
AIDS-related infections	

and do not warrant extensive diagnostic evaluations, less common causes should be considered when the child does not improve or respond to treatment.

The differential diagnosis for chronic cough in a child is extensive but can be organized in broad categories (Table 2).^{1–6} Diagnosis requires a careful history that covers general health, growth and development, environmental factors/triggers, associated symptoms,

Table 3. Suggested Diagnostic Studies for Common Causes of Chronic Cough in Children

Causes of Chronic Cough	Studies
Gastroesophageal reflux disease	pH probe study, isotope milk scan
Cystic fibrosis	Sweat test, DNA analysis/genetic evaluation
Inhaled foreign body	Chest radiography, rigid or fiberoptic bronchoscopy
Infection	Complete blood count, chest radiography, PPD test
Tracheomalacia	Fiberoptic bronchoscopy
Vascular ring	Chest radiography, barium swallow, fiberoptic bronchoscopy, CT scan of chest
Immune deficiency	Immune function testing, HIV testing
Vocal cord dysfunction	Laryngoscopy, fiberoptic bronchoscopy
Bronchiectasis	CT scan of chest
Chronic sinusitis with or without postnasal drip	CT scan of head, nasopharyngeal laryngoscopy

CT = computed tomography; PPD = purified protein derivative (tuberculin).

and a personal and family history of respiratory diseases.^{1,2} A thorough physical examination can be invaluable in narrowing the diagnosis by revealing signs of respiratory distress (retractions, grunting, nasal flaring), adventitious lung sounds (stridor, wheezing, rales), clubbing, cyanosis, chest size/shape, signs of atopy (rash, allergic shiners, nasal discharge, polyps), and cardiac murmurs.^{1,2} Although most children with a cough will not require an extensive work-up, if the etiology is not apparent from the initial evaluation, a tailored approach to further diagnostic testing should be employed based on the suspected diagnosis (Table 3).^{1–5} Common indications for ordering a chest radiograph include persistent cough (> 6 weeks), initial presentation of wheezing, cyanosis, examination suggestive of pneumonia or pulmonary edema, suspected foreign body aspiration, chest pain, trauma, and suspicion of underlying lung disease (ie, tuberculosis). Callahan³ examined referrals to a pediatric pulmonologist and confirmed that only in rare instances does the diagnostic evaluation of cough require procedures or tests not readily available to primary care physicians. A number of findings in the case patient suggested that further evaluation was needed, including the 2-month duration of cough and wheeze despite treatment, increasing difficulty with feeding, respiratory distress with intercostal and supraclavicular retractions, wheezing with bibasilar crackles, tachycardia, lack of tachypnea, and hypoxia.

Table 4. Complete Blood Count and Rapid Respiratory Panel for the Case Patient

Study	Result	Normal Values
Complete blood count		
Leukocyte count ($\times 10^3/\mu\text{L}$)	13.8	5.0–19.5
Segmented neutrophils (%)	21	20–48
Absolute neutrophil count ($\times 10^3/\mu\text{L}$)	2698	> 1800
Lymphocytes (%)	66	30–85
Atypical lymphocytes (%)	3	0
Monocytes (%)	10	5–20
Erythrocyte count ($\times 10^6/\mu\text{L}$)	3.33	3.1–4.5
Hemoglobin (g/dL)	9.6	9.5–13.5
Hematocrit (%)	29.6	29–41
Mean corpuscular volume, μm^3	89	74–108
Red cell distribution width (%)	14.4	11.4–14.5
Platelet count ($\times 10^3/\mu\text{L}$)	241	150–400
Rapid respiratory panel		
Respiratory syncytial virus	Negative	Negative
Parainfluenza types 1,2, and 3	Negative	Negative
Influenza types A and B	Negative	Negative
Adenovirus	Negative	Negative
<i>Bordetella pertussis</i> PCR	Negative	Negative
<i>Chlamydia</i>	Negative	Negative

PCR = polymerase chain reaction.

Key Point

Most children with cough will not require a work-up beyond a thorough history and physical examination. Only in rare instances does the diagnostic evaluation of cough require procedures or tests not accessible to primary care physicians.

DIAGNOSIS OF CASE PATIENT

Laboratory and Imaging Studies

Based on the initial history and physical examination, the patient was admitted to the general pediatric floor and initially managed as having an asthma/reactive airway disease exacerbation, although pneumonia and other infectious etiologies could not be ruled out. A complete blood count with manual differential and rapid respiratory panel were completed, and all results were within normal limits (Table 4). Posterior-anterior (PA) and lateral view chest radiographs were obtained (Figure 1). The radiographs were significant for a right-sided density consistent with a right aortic arch and were interpreted as otherwise normal.

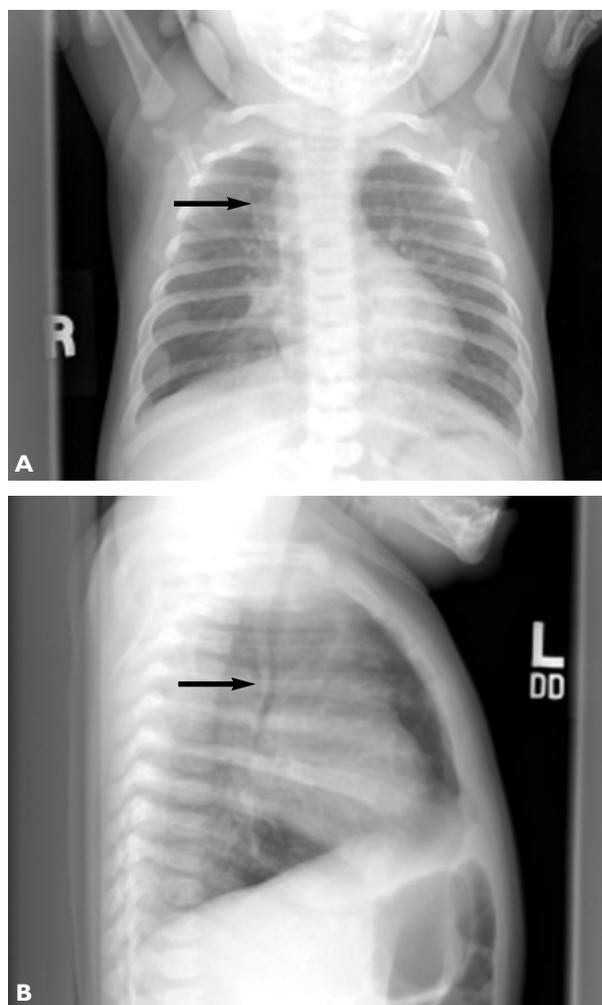


Figure 1. Posterior-anterior (PA) and lateral views of the chest. On the PA view (A) note the soft tissue density to the right of the sternum (arrow). There is a posterior indentation of the trachea on the lateral view (B) (arrow).

Hospital Course

The patient underwent further evaluation of the aortic arch abnormality, including a cardiology and cardiovascular surgery consult. Her electrocardiogram (ECG) and transthoracic echocardiogram were normal. An esophagogram with barium swallow confirmed the diagnosis of right-sided aortic arch (Figure 2). During her hospital stay, she successfully underwent a corrective surgical procedure, including division of the ligamentum arteriosum and adhesive bands surrounding the esophagus via a left thoracotomy through the fourth intercostal space. Her bibasilar crackles and hypoxia were thought to be a result of aspiration pneumonitis from her frequent episodes of emesis preceding her admission. At follow-up

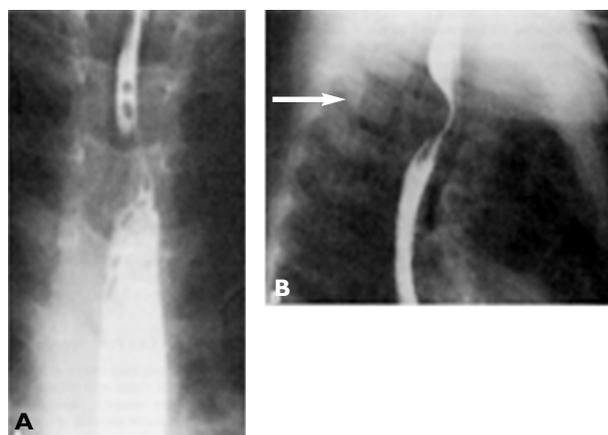


Figure 2. Barium esophagograms demonstrating vascular rings. (A) Posterior-anterior view (B). Lateral view. Note the indentation from the compression of the esophagus (arrow).

2 months later, she was free of cough and respiratory symptoms.

VASCULAR RINGS

Vascular rings have been described in the literature since 1737. The term vascular ring was coined by Gross in a 1945 *New England Journal of Medicine* article describing his successful division of a double aortic arch. Today the term refers to a collection of anomalous configurations of the aortic arch and its associated vascular structures that encircle and constrict the trachea and/or esophagus. In normal embryologic development, the 6 embryonic branchial arches either progress to form major vascular structures or involute. Vascular rings usually form when arches fail to involute (Table 5). In 1948, Edwards used embryologic, pathologic, and radiologic criteria established by Klinkhamer and Stewart to develop the classification system in use today.⁷

Vascular rings comprise less than 1% of all congenital cardiac abnormalities. Both sexes are affected equally, and no association with race or geographic location has been identified. Recent studies have suggested a link between vascular rings and deletions in band 22q11, which has already been associated with other cardiac abnormalities.⁷ Table 6 reviews the common types of vascular rings^{7–10}; the following discussion focuses on right-sided abnormalities.

RIGHT-SIDED AORTIC ARCH ABNORMALITIES

There are 2 major forms of vascular ring associated with the right-sided aortic arch. The most common presentation is a right aortic arch with aberrant origin of the left subclavian artery and a left-sided ductus

Table 5. Embryonic Branchial Arches

Primitive Arch	Developmental Destination
First	Arterial supply to face
Second	Arterial supply to face
Third	Carotid arteries
Fourth	
Right proximal	Proximal right subclavian artery
Right distal	Involutes
Left	Aortic arch
Fifth	Involutes
Sixth	
Right ventral	Proximal right pulmonary artery
Left ventral	Left pulmonary artery
Dorsal	Ductus arteriosus

Note: The distal right subclavian artery and left subclavian artery arise from the seventh segmental arterial branches of the dorsal aorta.

arteriosus (Figure 3). The other is a right aortic arch with mirror-image branching of the brachiocephalic vessels and the left innominate, common carotid, and right subclavian arteries.

Clinical Presentation

The presentation of vascular rings in children can vary widely, from incidental findings in an entirely asymptomatic patient to severe respiratory distress in a newborn. Most patients with right-sided abnormalities will present early in infancy. Adults with vascular rings typically are identified by incidental findings during cardiac catheterization, on chest radiographs, or on computed tomography scans or have been misdiagnosed with asthma.^{11,12} The most common complaints of symptomatic children are often nonspecific and include cough (sometimes described as seal-like), dyspnea, stridor, wheezing, recurrent upper respiratory tract infections, choking spells, emesis, and dysphagia. More severe symptoms and signs can include apneic episodes, cyanosis, and a toxic-appearing child.^{10,13} Because most symptomatic children will present to their primary care office with relatively vague complaints, it is important to keep vascular rings in the differential so that accurate diagnosis and treatment are not delayed. Although stridor is considered a hallmark, the presentation in this case was atypical in that stridor was absent.

Key Point

Most symptomatic children with vascular rings present with nonspecific complaints such as cough, wheeze, or emesis.

Table 6. Review of Vascular Rings

	Defect	% of Cases	Complete Ring?	Symptomatic?	Association with Other Cardiac Defects?
Double aortic arch	Failed involution of distal right fourth arch	85–95*	Yes	Yes, often severe	Yes (~22% of patients)
Anomalous left subclavian artery ± right aortic arch [†]	Involution of left fourth arch with persistence of right fourth arch	85–95*	Yes	Yes	Yes
Right aortic arch with left ligamentum arteriosum [†]	Involution of left fourth arch with persistence of right fourth arch	85–95*	Yes	Varies	Yes
Right aortic arch with mirror image branching	Partial involution of left fourth arch with persistence of right fourth arch	< 1	No	No	Yes (~98% of patients)
Left ligamentum arteriosum and aortic arch with retroesophageal right subclavian artery [‡]	Right subclavian artery arises as last brachiocephalic branch of descending aorta	< 1	No	Usually no	No
Left aortic arch with right-sided descending aorta	Atretic right aortic arch persists	< 1	Yes	Usually no	No
Left aortic arch with right-sided ligamentum arteriosum	Right subclavian artery arises more distally as a branch of right-sided aorta	< 1	Yes	Usually no	No
Anomalous left pulmonary artery (pulmonary sling) [‡]	Sixth arch development failure causing left pulmonary artery to arise as branch of right pulmonary artery	< 1	No	Varies	Yes (40%–50% of patients)

*These 3 anomalies combined account for 85% to 95% of vascular ring cases.^{8–11}

[†]These 2 anomalies are often found together as a single entity but have been described separately.

[‡]Although innominate artery compression syndrome and pulmonary artery sling are not complete anatomic “rings,” they are classified with the classic vascular rings because of the similarities in patient presentation, diagnosis, and surgical treatment.

Data from Bakker et al,⁷ Morrow,⁸ Kocis et al,⁹ and Moes and Freedom.¹⁰

Associated Abnormalities

While most patients will have isolated vascular ring findings, right-sided arch abnormalities are associated with a spectrum of cardiac and noncardiac syndromes. A recent study has shown that a band 22q11 deletion, already known to cause the CATCH 22 syndrome (DiGeorge, velocardiofacial and conotruncal anomaly face syndrome), may be seen in 20% of patients with right-sided arch vascular rings.¹⁴ There have also been proposed associations with other syndromes, including VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) and CHARGE (posterior coloboma, heart defect, choanal atresia, retardation, genital, ear), although further studies are currently underway. Of the cardiac abnormalities, the one most commonly associated with right-sided arch defects is ventricular septal defect, but associations have been suggested with other abnormalities, such as Tetralogy of Fallot.¹⁴

Diagnosis

A careful history and physical examination can

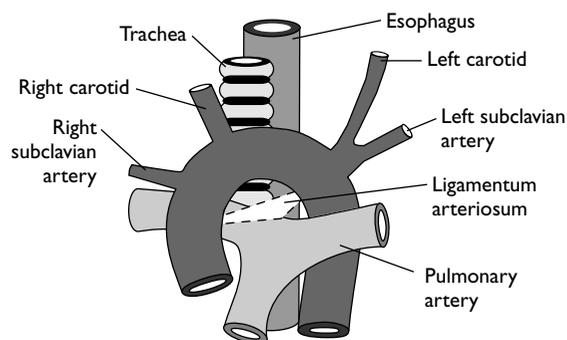


Figure 3. Right aortic arch with aberrant left subclavian artery and left ligamentum arteriosum. Note that dashed lines represent structures hidden by overlying structures.

reveal clues suggestive of right-sided aortic arch abnormalities. A complete blood count with differential and respiratory viral panel can be useful in determining the presence of an infection, although infection does not reliably rule out vascular rings because of high comorbidity rates. Currently, genetic testing for chromosomal

abnormalities is not routinely recommended unless there are highly suspicious findings on physical examination or a strong family history, although this recommendation may change in the near future.¹⁴

Chest radiography is the recommended initial study of choice for several reasons. Although some vascular rings may be missed on plain radiographs, other causes of respiratory distress such as pneumonia or tuberculosis can be diagnosed. Both PA and lateral view radiographs are needed for optimal evaluation. The PA view may show the displaced location of the aortic knob, normally seen as a soft tissue structure to the left of the sternum and a deviation of the lower trachea to the left. Posterior indentation of the trachea at the level of the aorta can sometimes be visualized on the lateral view.¹⁵ Pickhardt et al¹⁵ examined preoperative chest radiographs in 41 children with symptomatic vascular rings and found that none of the children had a normal radiograph. They suggest that a normal chest radiograph is a reliable study for excluding vascular rings in symptomatic children, although other studies recommend pursuing further evaluation if suspicion is high. The authors noted that the chest radiograph was not reliable in distinguishing between types of aortic vascular rings.¹⁵

Key Point

Initial work-up of vascular rings should include a complete blood count, respiratory panel, and PA and lateral chest radiographs.

Although angiography has been the gold standard for diagnosis and classification of vascular rings, magnetic resonance imaging (MRI) has clearly surpassed angiography as the diagnostic imaging study of choice, largely because it provides noninvasive visualization of the arterial branching patterns, tracheal and esophageal location and severity of obstruction, and cardiac anatomy. With the recent advances in 3-dimensional reconstruction, MRI is proving to be useful in preoperative planning. Despite the advantages over traditional angiography and computed tomography scanning, MRI is not routinely used in some locations because of its prohibitive cost, long waiting time, and need for increased amounts of sedation in the pediatric population.^{16,17}

Because many patients present with gastrointestinal symptomatology, it is not uncommon for vascular rings to be diagnosed by barium esophagography. Common findings include a right-sided indentation in the esophagus from a PA view and posterior indentation from the lateral view. Although some physicians routinely use the barium esophagogram as a follow-up to

a suggestive chest radiograph or echocardiogram, many now consider MRI a better imaging choice.^{16,17}

Because some vascular rings can be missed entirely using echocardiography, echocardiograms are not routinely performed unless other cardiac pathology is suspected. With increasing use of color Doppler flow technology, echocardiography may become more useful in the future.

Most patients have a normal ECG because there are no characteristic ECG findings in vascular rings in the absence of an associated cardiac abnormality. Cardiac procedures are not routinely recommended in the evaluation of patients with vascular rings. Rarely is there a need for cardiac catheterization without an associated cardiac abnormality. Some surgeons prefer to perform bronchoscopy rather than MRI prior to operating in order to visualize the tracheal abnormalities. It is more common to use bronchoscopy post-surgically (before leaving the operating room) to confirm that tracheal compression has been relieved.¹⁶

Key Point

Isolated vascular rings do not cause ECG abnormalities.

Treatment

Treatment of vascular rings is reserved for symptomatic patients and is primarily surgical. The goal of surgery is to relieve the esophageal and tracheal compression by dividing the vascular ring. Patients with a right aortic arch and left-sided ductus arteriosus or ligamentum arteriosum typically undergo a left posterolateral thoracotomy. While most patients undergo an open thoracotomy, video-assisted thoracoscopic techniques are becoming increasingly popular, as they appear to be as effective as open surgery with decreased healing time because of the less invasive nature of the surgery.¹⁸ The ductus/ligamentum is divided with dissection of any remaining fibrous bands surrounding the trachea and esophagus. If the dissection alone does not relieve the compression, arterioplexy of the aberrant left subclavian artery can be performed. Other less commonly used surgical approaches include right thoracotomy and median sternotomy. Use of cardiopulmonary bypass is limited to cases involving concurrent repair of an associated cardiac abnormality.¹⁸

Key Point

Only symptomatic vascular rings should be treated, and the treatment of choice is surgery.

Outcome/Prognosis

In patients with isolated vascular rings, there is essentially no operative mortality and few postoperative complications.^{18–20} If concurrent anomalies exist, the mortality rate is generally associated with the coexisting condition. Because symptoms are directly related to tracheal and esophageal compression, many postoperative patients will have immediate relief of symptoms. In younger patients and in patients with severe preoperative symptoms, there may be a delay in symptomatic relief. Typically, patients do well after surgical correction. Between 70% and 97% of children are entirely asymptomatic following surgery.^{19,20} The most common postsurgical complaints are persistent upper and lower respiratory symptoms.^{19,20} Tracheomalacia is most likely to occur in the very young; however, because these patients are well known to be more susceptible in the preoperative period, it is not entirely clear whether the surgical correction should be implicated. Rare operative complications include thoracic duct injury leading to chylothorax, phrenic nerve injury leading to diaphragmatic paresis or paralysis, and recurrent laryngeal nerve injury leading to vocal cord paresis or paralysis.¹⁸ Marmon et al²¹ studied pulmonary function after repair of vascular rings and slings and found that while most children will be asymptomatic, a few may have persisting physiologic airway obstruction detectable by spirometry. Because even the patients with persistent defects were asymptomatic, it is unclear whether the findings have any clinical significance. Currently, following asymptomatic children with pulmonary function testing is not recommended. Some studies suggest that patients with persistent symptoms should be further evaluated with pulmonary function tests, MRI, and bronchoscopy. In severe cases patients may require aortopexy.^{20,21} In some studies, up to 30% of children continue to have persistent cough thought to be related to tracheal injury. In children who had reflux disease detected on barium esophagram, there was an increased risk of persistent reflux symptoms after surgical correction of the vascular ring, which could often be treated successfully with supportive care or medical intervention.²¹

Key Point

Patients without tracheomalacia are asymptomatic shortly after surgery and do not need frequent follow-up testing as long as they remain asymptomatic.

CONCLUSION

Vascular rings are an uncommon but clinically significant cause of respiratory and gastrointestinal symptoms

in children. Because children with vascular rings often present with vague symptoms that mimic more common disorders, misdiagnosis is common. Physicians should keep the diagnosis in the differential of those patients who fail to respond to initial therapy. Early diagnosis prevents patients from being subjected to unnecessary interventions and therapies and allows them access to safe reliable surgical intervention. **HP**

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