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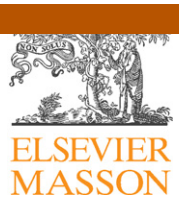

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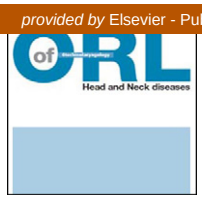

UPDATE

Pathophysiology and diagnostic approach to laryngomalacia in infants

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KEYWORDS
Laryngomalacia;
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Summary Laryngomalacia is defined as collapse of supraglottic structures during inspiration. It is the most common laryngeal disease of infancy. Laryngomalacia presents in the form of stridor, a high-pitched, musical, vibrating, multiphase inspiratory noise appearing within the first 10 days of life. Signs of severity are present in 10% of cases: poor weight gain (probably the most contributive element), dyspnoea with permanent and severe intercostal or xyphoid retraction, episodes of respiratory distress, obstructive sleep apnoea, and/or episodes of suffocation while feeding or feeding difficulties. The diagnosis is based on systematic office flexible laryngoscopy to confirm laryngomalacia and exclude other causes of supraglottic obstruction. Rigid endoscopy under general anaesthesia is only performed in the following cases: absence of laryngomalacia on flexible laryngoscopy, presence of laryngomalacia with signs of severity, search for any associated lesions prior to surgery, discrepancy between the severity of symptoms and the appearance on flexible laryngoscopy, and/or atypical symptoms (mostly aspirations). The work-up must be adapted to each child; however, guidelines recommend objective respiratory investigations in infants presenting signs of severity.

Laryngomalacia is defined as collapse of supraglottic structures during inspiration. Clinical practice guidelines for congenital laryngomalacia were published by the SFORL in 2011. This article describes the diagnostic approach to congenital laryngomalacia.

Pathophysiological mechanisms of laryngomalacia in infants

Not all neonates have the same laryngeal anatomy, but all neonates potentially present supraglottic structures that can invaginate during inspiration. The development of symptoms results from variable combinations of the infant's specific laryngeal anatomy, poor control of the tone of supraglottic structures (either pathological neurological mechanisms or simple physiological variations related to changes in tone during sleep), mucosal oedema, and increased airflow (Fig. 1).

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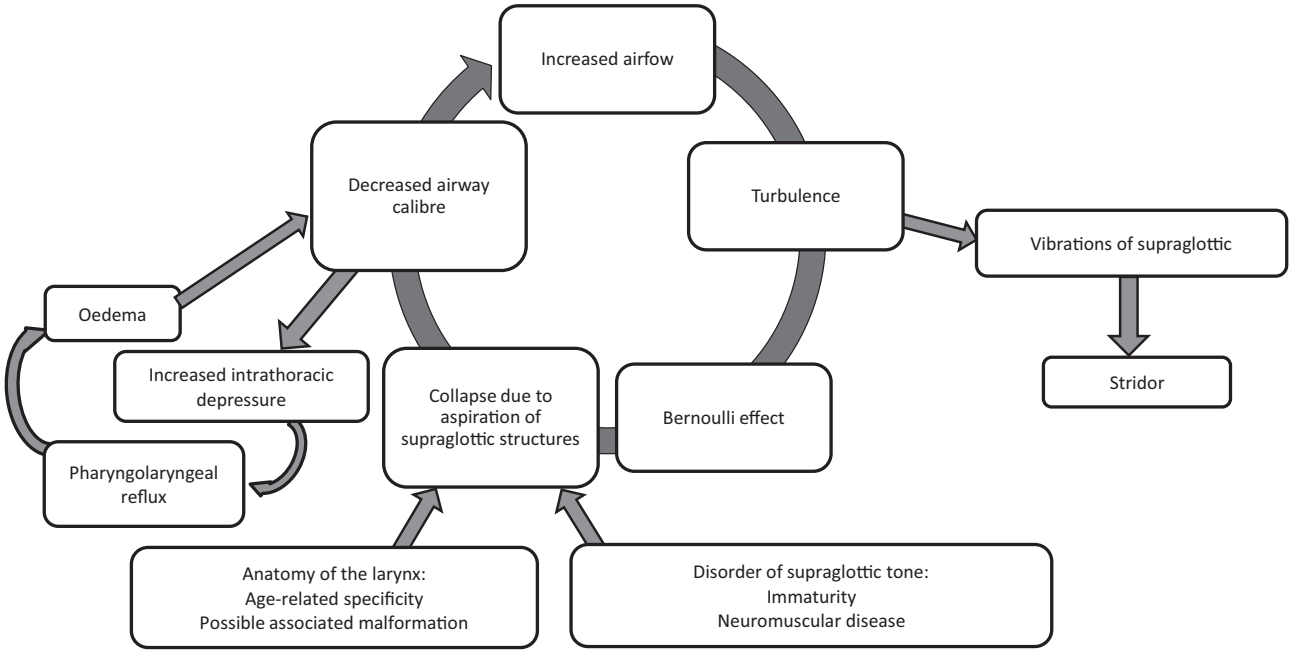

Figure 1 Pathophysiology of laryngomalacia. $\int$ Larynx anatomy + neurological state + gastro-oesophageal reflux disease (GERD) + Airflow = Symptoms.

The anatomy of the neonatal larynx presents a number of specificities, as the epiglottis is relatively longer (compared to the length of the larynx) than in older children and can be tubular, or even omega-shaped. The infant's epiglottis can therefore prolapse posteriorly and participate in collapse of the supraglottis. Aryepiglottic folds are long, with relatively large, flaccid mucosa. These folds may be short in the anteroposterior plan, drawing the epiglottis posteriorly. Aryepiglottic folds can prolapse medially and inferiorly into the supraglottis, narrowing its lumen. They can also vibrate. Manning et al. showed that the aryepiglottic folds are significantly shorter in infants with severe laryngomalacia than in infants with no signs of severe laryngomalacia [1]. The corniculate cartilages and the superior part of the arytenoid cartilages are clearly visible in the posterior part of the supraglottis, giving the impression of a deep supraglottic interarytenoid groove. These cartilages can prolapse anteriorly and inferiorly into the airway and can also vibrate. During the first 18 months of life, the supraglottis lengthens less rapidly than the rest of the larynx (while the growth of the supraglottic and subglottic airways is identical) [2]: the anatomical structure predisposing to laryngomalacia therefore disappears around the age of 18 to 24 months (Fig. 2).

Mucosal oedema has been demonstrated histologically [3] and participates in narrowing of the airway. This oedema is related either to pharyngolaryngeal reflux (PLR) or mucosal trauma during inspiration. Severe laryngomalacia induces intercostal retraction with increased intrathoracic depression, which, in turn, predisposes to gastro-oesophageal reflux disease (GERD), increasing the mucosa oedema, creating a self-perpetuating process.

The clinical features can be influenced by disorders of neuromuscular tone. Some forms of laryngomalacia are more severely (or exclusively) symptomatic during sleep. The concept of laryngeal immaturity is contested, as laryngomalacia is not more frequent in preterm infants [4] [5]. Documented neuromuscular disease (congenital or acquired with hypotonia and/or psychomotor retardation) can be present with a prevalence varying according to the series between 8 and 50% [6]. The prevalence of neuromuscular disease is higher in the case of severe laryngomalacia and influences the results of surgery [7]. In this setting, laryngomalacia may not be isolated, but part of a broader syndrome of pharyngolaryngomalacia. Moreover, acquired laryngomalacia due to an acquired neurological abnormality (stroke, degenerative disease, tumour) is well known [8].

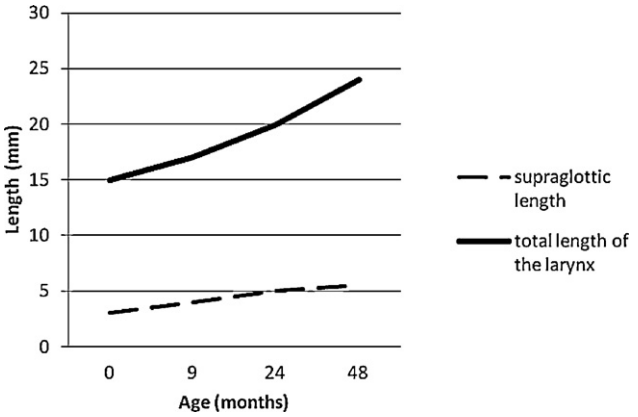

Figure 2 Course of the length of the supraglottis during growth. Post-mortem anatomical study of four larynges [2] — the supraglottis grows less rapidly than the larynx as a whole.

What is known about the epidemiology of laryngomalacia in infants and associated lesions?

The real incidence of laryngomalacia is unknown, although it is the most common cause of stridor in infants. The incidence has been estimated in cohorts of infants with stridor referred for specialist consultation: these studies did not include infants with mild permanent or intermittent stridor. For example, Zoumalan et al. [9] published a series of 202 infants under the age of 12 months examined for stridor in a specialized unit: stridor was present at birth in 157 infants and 94% of them had laryngomalacia.

The prevalence of associated airway lesions has been more clearly documented: such lesions are present in 18.9% of cases according to Mancuso et al. [10]. Associated laryngotracheal lesions (laryngeal dyskinesia, vocal cord paralysis, subglottic stenosis, tracheomalacia) are more frequent in infants with severe laryngomalacia: Dickson et al. [11] reported associated lesions in 79% of cases of severe laryngomalacia (including 73.3% of subglottic stenosis and 55.3% of tracheomalacia) and in 28.8% of cases of laryngomalacia with few signs of severity. Schoeder et al. reported similar figures [5]. Other airway lesions may also be observed: pharyngeal obstruction (including microretrognathism, glossoptosis, vallecular cyst, palatal anomaly) or nasal obstruction (choanal atresia) [6]. These anomalies can be part of a syndrome (Down syndrome, CHARGE). For example, laryngomalacia is observed in 50% of trisomic infants [12].

Cardiac anomalies may also be observed in 31% of cases, according to some authors [13], in line with the 51% of cardiac anomalies reported in patients with congenital laryngeal diseases (ASD, VSD, patent ductus arteriosus, PHT) by Sakakura et al. [14].

Clinical presentation of laryngomalacia

Although variants of laryngomalacia have been described in older children and adolescents [6], laryngomalacia usually presents rapidly, during the first 10 days of life. It is characterized by stridor which is a high-pitched, musical, vibrating, multiphase inspiratory noise. A hoarser tone or later onset of stridor should raise the suspicion of another aetiology. The stridor of laryngomalacia is often worsened by agitation, crying, feeding, and flexion of the cervical spine, and is often improved by extension of the cervical spine, the prone position and quiet breathing. The intensity of stridor is variable during sleep, increasing or decreasing according to the infant. Stridor usually deteriorates during the first months of life, followed by slow improvement after the age of one year, but stridor can sometimes persist for several years [15].

Laryngomalacia with no signs of severity

Most forms of laryngomalacia are minor (70—90%) causing isolated and intermittent stridor, with no changes of crying or coughing, no dyspnoea, and no swallowing disorders [16]. These minor forms have no consequences on the infant's growth. The loudness of stridor does not appear to be proportional to the severity of laryngomalacia and some infants can have very severe laryngomalacia with no real stridor. Moreover, parents must be warned that stridor usually becomes louder between the ages of 0 and 4 months. Tracheal tug is frequent, but is not a sign of severity. This clinical presentation is not pathognomonic of laryngomalacia. Other diseases requiring specific management may present with the same clinical features: only systematic office flexible endoscopy performed in visit can confirm the diagnosis of laryngomalacia.

Signs of severity of laryngomalacia

Signs of severity are:

- poor weight gain (probably the most contributive element);
- dyspnoea with permanent and severe intercostal or xyphoid retraction;
- episodes of respiratory distress;
- obstructive sleep apnoea;
- episodes of suffocation while feeding or feeding difficulties.

Ten to 20% of cases present signs of upper airway obstruction due to the supraglottic obstacle: episodes of cyanosis particularly while feeding, dyspnoea with intercostal retraction, progressive chest deformity (pectus excavatum) [17]. Apart from signs of GERD (regurgitation, vomiting, malaises, etc.), feeding disorders can also comprise micro-aspirations and slow feeding. When feeding disorders are predominant, an associated disease must be excluded. Chronic airway obstruction induces an increase in the infant's energy expenditure, which, combined with feeding disorders, results in poor weight gain or even muscle atrophy. The most severe forms present features of chronic respiratory failure, sometimes responsible for pulmonary artery hypertension and heart failure [18].

Clinical and complementary work-up strategy

The work-up has a triple objective:

- to confirm the diagnosis of laryngomalacia by systematic flexible laryngoscopy whenever laryngomalacia is suspected;
- to identify associated lesions by clinical examination;
- to determine the severity of laryngomalacia and its repercussions by complementary examinations, in the presence of clinical signs of severity.

To confirm the diagnosis of laryngomalacia

Despite the specific features of the stridor usually associated with laryngomalacia, clinical diagnosis based on listening to the infant's breathing is not absolutely reliable [19] and must be confirmed by direct visualization of the larynx.

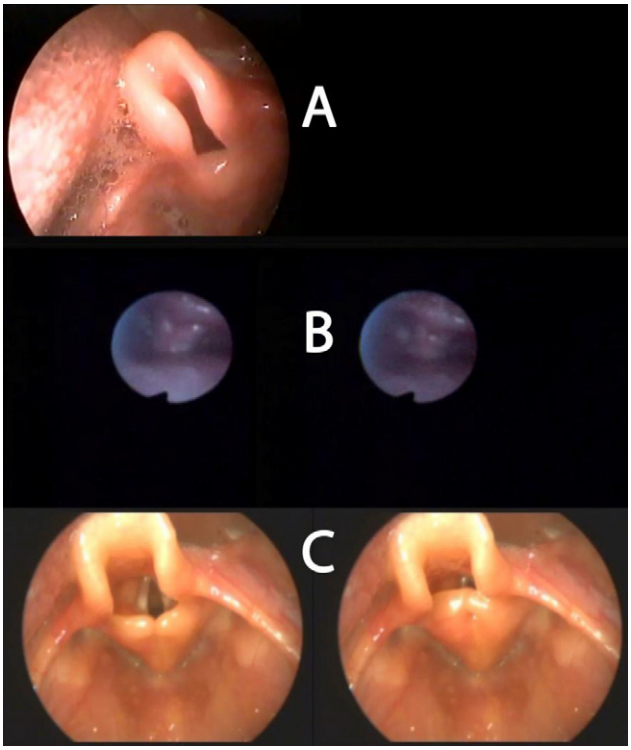

Figure 3 Examples of endoscopic findings in laryngomalacia. A. Supraglottic stenosis with tubular epiglottis and short aryepiglottic folds. B. Anterior laryngomalacia with complete collapse of the marginal zone of the epilarynx totally masking the glottis. C. Posterior laryngomalacia with anterior prolapse of the corniculate cartilages (right photograph).

Flexible laryngoscopy must be performed systematically: the positive diagnosis of laryngomalacia requires dynamic examination of the larynx in a conscious infant.

In the great majority of cases, this examination is performed in the office via the nose with or without local anaesthesia (5% lidocaine is not approved for children under the age of 6 years — do not exceed one puff per 10 kg of body weight), or via the mouth, without entering the glottis. The presence of stridor during laryngoscopy is necessary to confirm the diagnosis.

In an infant with a risk of cardiorespiratory malaise, flexible laryngoscopy must be performed in an environment equipped with resuscitation equipment.

The usual endoscopic findings are (Fig. 3):

- visualization of more or less complete collapse of the supraglottis concomitant with stridor, during inspiration, which can obstruct visualization of the glottis with short aryepiglottic folds;
- anterior prolapse of the arytenoid cartilages and possibly the corniculate cartilages (accessory or sesamoid cartilages);
- posterior prolapse of the epiglottis which can be curled up to form a tubular structure. An omega-shaped epiglottis is not necessarily pathological [20].

Classifications of the various types of laryngomalacia have been proposed. Holinger's classification is indicated below [20]:

- Type 1: anterior prolapse of the arytenoid and corniculate cartilages;
- Type 2: tubular epiglottis which curls on itself, often associated with type 1;
- Type 3: anteromedial collapse of the arytenoids;
- Type 4: posterior prolapse of the epiglottis;
- Type 5: short aryepiglottic folds.

Flexible laryngoscopy must exclude associated glottic or supraglottic obstruction. Visualization of the glottis, particularly the essential evaluation of mobility of the glottis, can sometimes be difficult. Video recording allowing review of the examination provides a major contribution.

Rigid endoscopy under general anaesthesia must not be performed systematically, but is necessary to investigate the subglottis and the entire airways in the following situations:

- absence of laryngomalacia during fiberoptic laryngoscopy;
- presence of laryngomalacia with signs of severity: investigation of any associated lesions is part of the anatomical work-up prior to surgery;
- discrepancy between the severity of the symptoms and the appearance on fiberoptic laryngoscopy;
- atypical symptoms suggestive of laryngeal diastema (predominant aspirations) or oesophagotracheal fistula (aspirations, abdominal bloating, associated pneumonia, etc.).

Subglottic and tracheal examination is usually performed under general anaesthesia with spontaneous breathing, generally using a rigid laryngoscope or possibly a rigid bronchoscope. Some teams perform fiberoptic laryngotracheal endoscopy under local anaesthesia in a specialized environment.

Examination under general anaesthesia does not allow a precise diagnosis of laryngomalacia and may miss associated laryngeal palsy. When fiberoptic laryngoscopy in the conscious infant does not reveal any obvious laryngomalacia, the presence of sleep-induced laryngomalacia may be observed during the general anaesthetic induction phase.

One study reported a false-negative rate of about 8% for fiberoptic laryngoscopy performed without anaesthesia [21] (based on double-blind reading of 140 silent videos of laryngoscopy performed either in a conscious infant or under general anaesthesia; control videos of infants with no laryngeal lesion were also analysed). The double-blind methodology of this study is attractive, but the absence of audio information associated with the videos may have increased the false-negative rate.

No strict correlation has been established between a particular of type laryngomalacia and the severity of laryngomalacia. However, complete laryngeal collapse preventing visualization of the glottis can be considered to be a sign of severity (expert opinion). Standard radiography is no longer indicated since the availability of fiberoptic laryngoscopy. A bayonet appearance of the trachea is not pathological.

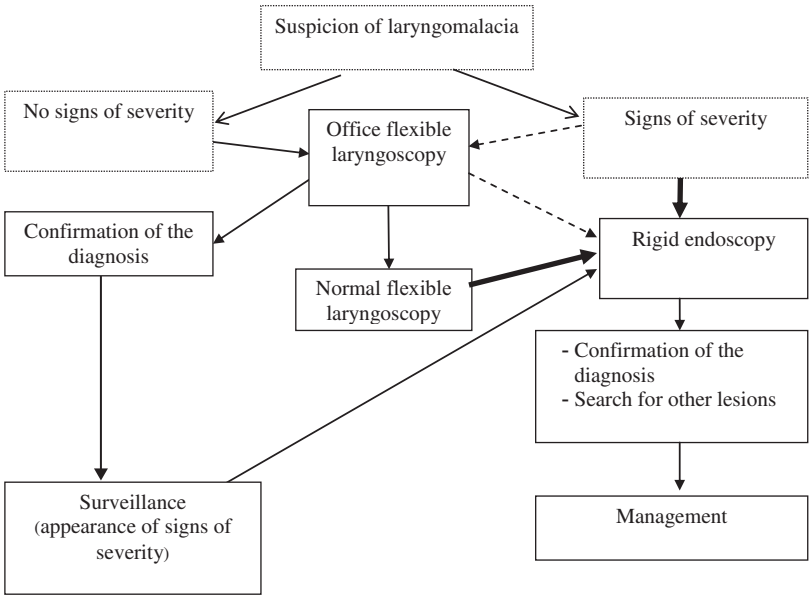

Figure 4 Laryngomalacia — Decision flow-chart.

To identify associated lesions by clinical examination

Clinical interview must detect the presence of symptoms of GERD. Flexible laryngoscopy provides arguments in favour of pharyngolaryngeal reflux (PLR): oedema or erythema of the posterior wall of the larynx. The association between laryngomalacia and PLR has been largely demonstrated and is sufficiently significant not to require systematic investigations [22]. However, persistence of indirect endoscopic signs of PLR or clinical symptoms of GERD despite medical treatment may be an indication for oesophageal pHmetry.

A complete paediatric clinical examination is essential to detect associated comorbidities: retardation, multiple malformation syndrome (CHARGE, Pierre Robin sequence, Down syndrome, 22q11 deletion). The incidence of associated malformations is 8 to 50% [5,11,23].

To determine the severity of laryngomalacia and its repercussions by complementary examinations, in the presence of clinical signs of severity

No data are available concerning the indications for polysomnography in laryngomalacia.

The task force proposed polysomnography to guide therapeutic management in infants with cardiac or neurological or complex multiple malformation syndrome, as this examination can distinguish between the repercussions related to airway obstruction and those related to the associated comorbidity. It should also be performed in the case of failure of surgical management of laryngomalacia.

Measurement of PO_2 and PCO_2 evaluates the consequences on gas exchange in severe forms of laryngomalacia. Echocardiography is performed in infants with associated cardiac malformations or hypoxia (PHT). The other complementary investigations are discussed case by case (Fig. 4).

Atypical laryngomalacia: clinical features and principles of treatment

Late onset laryngomalacia

Acquired laryngomalacia has been occasionally described in the literature and can occur in both older children and adults. It has usually been described in the context of neurological events or coma and can be reversible in some cases, reinforcing the neuromuscular hypothesis of congenital laryngomalacia, although these acquired cases usually exclusively concern the epiglottis that becomes flaccid and able to invaginate between the vocal cords [24]. Some forms of laryngomalacia are induced by effort.

Pharyngolaryngomalacia (PLM)

Clinical features

In addition to the signs usually described in laryngomalacia, children with PLM also experience sleep-disordered breathing, usually associated with feeding difficulties related to swallowing disorders with aspirations and/or disorders of coordination of the suckling-swallowing reflex. GERD is frequently present, ideally demonstrated by dual-channel pHmetry. In the literature, few authors have specifically distinguished these cases of PLM, which are generally included in the group of laryngomalacia. When PLM is identified, it is rarely isolated and is usually part of a known or unknown congenital syndrome: neonatal brainstem dysfunction [25]. In the series reported by Froehlich et al. [26], 27 out of 82 infants presented PLM: three infants present an isolated form, 15 infants presented an identified syndrome (CHARGE, Down syndrome, neonatal anoxia, Ondine's curse) and nine infants presented a combination of anomalies not corresponding to a known syndrome. Furthermore, 18 infants (67%) presented neurological anomalies. The most common neurological anomaly was axial hypotonia, observed in 12

out of 18 cases. Radiological abnormalities (brain CT or MRI) were detected in eight cases of this series, consisting of cortical atrophy or microcephaly. PLM is frequently observed in CHARGE syndrome. In the review by Roger et al. [27], based on 45 infants with CHARGE syndrome, PLM was present in 61.4% of cases.

Endoscopic features

During rigid endoscopy under general anaesthesia, flexible fiberoptic laryngoscopy performed at the beginning of the procedure during induction of anaesthesia is essential to allow dynamic analysis of the larynx that may sometimes reveal abnormalities not identified during nasal fiberoptic laryngoscopy in the conscious patient. In PLM, inspiratory collapse of the lateral walls of the pharynx is observed in the absence of any tonsillar hypertrophy, and may be associated with glossoptosis. In the larynx, laryngomalacia with collapse of the supraglottic larynx due to anteroposterior flattening of the larynx with prolapse of the arytenoids anteriorly and the epiglottis posteriorly is associated with PLM. Direct laryngoscopy of cases of PLM does not reveal short aryepiglottic folds or redundant supraarytenoid mucosa, thereby allowing the distinction with ''peripheral'' forms of laryngomalacia with an anatomical substratum.

Management

A general work-up looking for associated abnormalities must be performed in all cases of PLM. Brain MRI and pHmetry must be performed. Depending on the clinical findings, this work-up may be completed by cardiological, ophthalmological, genetic assessment, etc. Polysomnography must be performed to assess the severity of PLM and especially the degree of obstructive syndrome, in order to guide treatment in a context of noninvasive ventilation.

PLM has a variable course. Some forms, particularly isolated forms, can improve with time. Deterioration of breathing and/or feeding and/or neurological disorders have also been observed with no correlation between the course of these three spheres [26].

Conclusion

Laryngomalacia is the most common laryngeal disease in infants, although its epidemiology has been poorly defined. The diagnosis is essentially based on office flexible laryngoscopy, which confirms laryngomalacia and excludes other causes of supraglottic obstruction. Laryngomalacia is usually well tolerated and has a favourable course in most cases. In 10% of cases, it is poorly tolerated with the presence of signs of severity: an assessment is then performed to guide treatment, which is usually surgical.

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