An Updated Review of Etiology and Pathogenesis of Laryngotracheal stenosis Role of Inflammatory Cytokines in the Development of Laryngeal Stenosis

[1]Abdelmaksoud G, [1]Mohamed Ahmed Alshawadfy Saleh, [1]Magdy Kamel Abdelmaksoud, [1]Sameh M Hosny, [2] Ayman A Allam, [2] Ahmed Elsadek Fakhr, [1]Marwa Abdelraouf Mohammed, [1]Tarek G Elnaggar

[1] Otorhinolaryngology, Head and Neck Surgery Department, Faculty of Medicine - Zagazig University, Zagazig, Egypt

[2] Microbiology Department, Faculty of Medicine - Zagazig University, Zagazig, Egypt

Abstract:
Adult laryngotracheal stenosis (LTS) is a potentially fatal condition that is challenging to recognise and manage. The cause of airway stenosis is unclear, and while a great number of patients benefit from routine surgical treatment, the recurrence rate is high. There aren't many medical treatments, yet the need is expanding. Even though LTS in adults is a complicated and difficult clinical condition, there is encouraging study of the disorder's inflammatory causes, which could provide ground-breaking new therapeutic options.

Keywords: Inflammation, laryngotracheal stenosis, subglottic stenosis, pathogenesis.

Tob Regul Sci. ™ 2022;8(1): 3490-3498
DOI: doi.org/10.18001/TRS.8.1.263

Introduction:

Laryngotracheal stenosis (LTS) means pathological narrowing of subglottic region of larynx and/or part of trachea. The cause of narrowing is excessively formed scar tissue and often leads to voice problems and/or difficult breathing in these patients. Extensive narrowing of the lumen may be a life-threatening condition causing obstruction of airway(1).

Etiology of laryngotracheal stenosis

Multiple etiologies of laryngotracheal stenosis are present including congenital and acquired causes such as trauma that may be external trauma (blunt or penetrating)or internal trauma (Prolonged intubation (iatrogenic), radiotherapy-induced, foreign bodies and causic ingestion), autoimmune disease, infections or idiopathic, but Iatrogenic and idiopathic reasons account for the majority of cases of lower extremity edoema (2).

Congenital long trachea syndrome is caused by a developmental failure of the standard procedure of complete re-canalization of the foetal airway during foetal life. This developmental failure typically takes place at the end of the third month of pregnancy and is typically accompanied by other congenital anomalies of the head and neck. Congenital stenosis can manifest itself in a

number of different ways, including a thin membranous stenosis, a thick anterior or posterior web (cartilage malformation), or even total fusion of the vocal cords (3).

Idiopathic LTS is fibrotic stenosis with a circumferential pattern within the region of the larynx that is subglottic and/or uppermost part of trachea, extending less than 2 cm in length, and more common affecting females. It appears without history or evidence of external trauma of laryngotracheal track, prolonged intubation, infection, autoimmunity or other identifiable cause of stenosis **(4)**.Estrogen level is considered as a cause and playing a role in development of fibrosis **(5)**.

Considered causes of hyperemia and edoema of mucosa with tracheal lumen narrowing are elevated oestrogen levels. On the tracheal fibroblasts of iSGS patients **(6)**, progesterone and oestrogen receptors have been identified. Gastroesophageal reflux illness has been proposed as a possible contributor to Idiopathic LTS **(7)**.

In iatrogenic stenosis, usually developed in Tracheal and posterior glottic sites after prolonged use of endotracheal tube sized more than 7.5 for more than ten days due to pressure effect causing tissue ischemia ,mucosal ulceration that healed by secondary intention and fibrosis, if pressure caused by the tube exceeds capillary perfusion pressure. It was found that movement of endotracheal tube due to ventilator effect and inadequate patient sedation is another factor predisposing to stenosis**.(8).**

Besides, there are some Comorbidities impacting wound healing negatively, such as diabetes, chronic smoking and COPD, were considered as factors contributing for stenosis of the glottis and related with iatrogenic LTS **(9).** The dysregulated mucosal wound repair that occurs after intubation is probably affected by the presence of intrinsic comorbidities. Through microvascular injury, which impairs wound healing and raises the risk of tracheal injury and long-term reliance on tracheostomy, diabetes is able to contribute to an increased likelihood of both of these outcomes **(10).** Epithelial and lamina propria damage due to smoking, results from decrease of blood supply making the area of airway more affected by mechanical injury.**(11).**

LTS has been linked to autoimmune disorders such as Wegener's granulomatosis (WG) (granulomatosis with polyangitis), cicatricial pemphigoid, sarcoidosis, and recurrent polychondritis (4). SGS can be caused by a number of autoimmune disorders, including Wegener's granulomatosis, which is one of them. Patients often have a positive result for antineutrophil cytotoxic antibody testing, which is indicative of a systemic inflammatory disease that is characterised by the development of necrotizing granulomas mixed with small to medium vasculitis across the entirety of the respiratory tract and kidneys (ANCA) (12).

It is hypothesised that autoimmune SGS develops as a result of the elimination of autoantibodies caused by inflammation of the subglottic extracellular matrix. This exposes the cricoid cartilage to the immune system, which then causes inflammation of the cartilage(13). Infections like scleroma, syphilis, tuberculosis, fungal infection and diphtheria can cause LTS at different sites. Tuberculosis usually affecting supraglottis and glottis but laryngoscleroma affects subglottic region causing chronic inflammation followed by fibrosis. **(14).**

Pathogenesis of laryngotracheal stenosis

Pathogenesis of LTS and how it is different between each etiology is not well understood and is thought to be a barrier to the development of LTS medication therapy. Due to the variety of the disease's aetiology, studies studying the pathophysiology of LTS are rare (9). Less is known about the mechanisms that underlie the pathophysiology of LTS. There are several explanations for the pathogenesis of SGS including alterations in oestrogen and oestrogen receptor levels, as well as microtrauma to the airway, were observed such as in cases of prolonged intubation causing compression and local tissue ischemia. However, these mechanisms do not explain the pathogenesis of other causes of airway stenosis **(15).**

Trachea is considered to be formed of three structures: mucosa, lamina propria and cartilage. Mucosa would heal by regeneration and regain its normal function and micro- architecture. So, if there is injury causing only mucosal ulceration, it could not generally lead to long term stenosis. This explains that only 1 from 10 patient with prolonged intubation develop stenosis **(16).**

Healing of lamina propria and cartilage usually is by fibrosis. So if there is injury causing Lamina propria damage, it could lead to excessive granulation tissue formation that cause airway obstruction, and progression to sub-mucosal fibrosis and mature scar formation. Wegener's granulomatosis, tuberculosis and laryngo-scleroma cause ulcerative trachea-bronchitis which causes lamina propria fibrosis. Deeper injuries that reach cartilage lead to perichondritis, cartilage necrosis and chondrolysis, which can cause structural collapse of cricoid and trachea **(17).**

Recent investigations suggest that in cases of iLTS, an initial epithelium and subepithelial insult results in prolonged and uncontrolled wound healing, creating a pathologic scar in the airway. **(9).**

Recent evidence of Mycobacterium-specific gene products and an immunological milieu in iSGS suggests that infection may be a cause of this condition, and alterations in the IL-17 signalling pathway suggest an immunological explanation for iSGS **(18).**

Based on the fact that LTS is chronic fibro-inflammatory disease and Given the postulated significance regarding the significance of the inflammatory response in the disease processes underlying both iLTS and iSGS is examined of a minimally invasive technology for assessing inflammation in human LTS would be crucial for advancing knowledge of the immune-pathogenesis of this disease. In addition, the existence of serial changes in inflammatory markers in both iLTS and iSGS will provide information on the development of the disease and may help the physician and patient determine treatment **(19).**

Diagnosis of subglottic stenosis:

History and physical examination:

Children with SGS fall into one of three categories: (1) intubated in the neonatal intensive care unit; (2) having a tracheotomy performed and a verified diagnosis of SGS; or (3) without an artificial airway, but with a history that points to SGS being the likely cause. The criteria for evaluation that are used for each of these different types of children are identical, with

minor variations based on presentation. Initially, a complete history is obtained. In addition to a comprehensive head and neck examination, the physical examination should also examine failure to thrive and developmental level (20).

The severity of respiratory issues should be assessed if the child is not tracheotomized or intubated. Good outcomes in the treatment of SGS may be hampered by other congenital illnesses of the upper airway, including as craniofacial anomalies, retrognathia, macroglossia, choanal atresia, laryngomalacia, and paralysis of the vocal cords. The chest should be listened to to see how much air is coming in, and the front of the neck should be listened to to see if airflow is restricted at a certain level in the upper airway (21).

Patients with iSGS in adults are virtually mainly Caucasian women. Between 30 and 60 is the typical age range. Exertional dyspnea, stridor, persistent cough, and wheezing are the most typical symptoms, with a mean diagnostic time of 19 months to 4 years. (22). Most of these symptoms appear when the stenosis has increased to more than 50% of the airway's diameter. Consequently, a substantial proportion of individuals with central airway stenosis and no risk factors are misdiagnosed with other respiratory disorders. It is hardly surprising that one-third of individuals are incorrectly diagnosed with asthma or COPD (23).

- **Laboratory investigations:**

Beside history and clinical examinations, laboratory investigations could be used. The aim of laboratory investigations to assess causes of SGS. They included ANCA P & C (if elevated suggest wegner), serum calcium, Serum angiotensin converting enzyme (ACE) level (if elevated suggest sarcoidosis) and inflammatory markers **(24).**

Radiological evaluation:

Chest x ray and CT chest and neck are of limited value in diagnosis of SGS. Chest x-rays can detect tracheal disease, foreign bodies, and other pulmonary issues, Multiplanar computed tomography (CT) is good for planning treatment and figuring out how far a disease has spread (25).

CT scans of the airway differ from those of the neck or chest in that thinner slices are taken for three-dimensional reconstruction. The three-dimensional exterior and internal airway pictures show a high level of sensitivity and specificity when compared to rigid bronchoscopy. In the case of dynamic collapse, like that seen in CT imaging during inspiration and expiration can show crescent-shaped changes linked to posterior membrane collapse in tracheobronchomalacia**(26).**

A 3D model using high resolution CT and multicolor model was reported to diagnose subglottic stenosis in some reports **(27, 28).**

MRI can be considered as An alternative to SGS that is non-invasive and radiation-free. Laryngoscopy during longitudinal laryngeal examinations may be supplemented with MRI follow up of SGS and can be used for staging of SGS **(29) (Figure 1)**

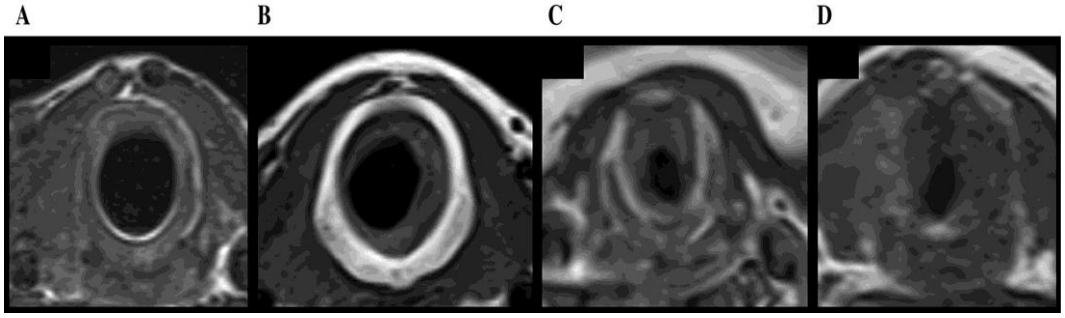

Figure (1): Staging of SGS using MRI technique **(29).**

Axial T1-weighted MRI of patients with confirmed WG and increasing grades of SGS. (a) a man without evidence of subglottic stenosis, (b) a man with a stenosis of 25%, (c) a woman with a stenosis of 58% and (d) a woman with a stenosis of 77% (29).

Endoscopic evaluation:

- **Flexible endoscopy:**

All non-intubated patients who might have a blocked airway obstruction should have a flexible fiberoptic nasopharyngoscopy done while they are awake. It is required to examine the nares, nasal cavity, naso-oro- and the hypopharynx, the supraglottis, and the glottis. Endoscopic examination of the front of the nose and nasopharynx makes it possible to check for and rule out nasal and nasopharyngeal disease (30).

Oral and hypopharyngeal visualisation measures hypopharyngeal tone and tonsil hypertrophy. The supraglottis is examined for edoema, erythema, or a cobblestone look, which are all signs of gastroesophageal reflux disease and laryngomalacia. (31).

It is crucial to investigate the actual movement of the vocal cords. This is performed most effectively with a flexible endoscope on a patient who is fully awake. A glimpse of the subglottis is visible, but a thorough examination of the subglottis requires rigid endoscopy under general anaesthesia **(32) (Figure 2).**

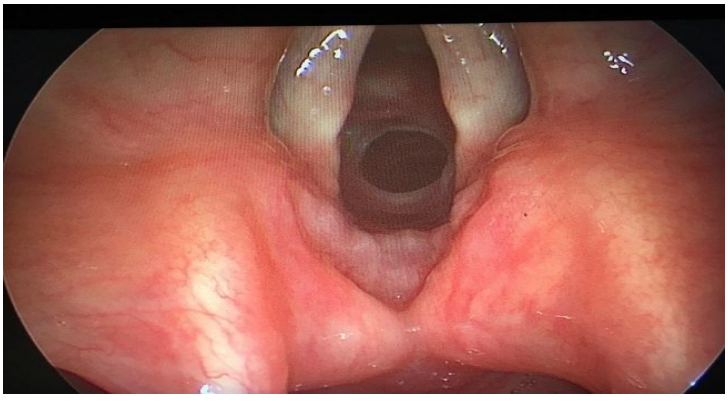

Figure (2): Broncoscopic view of the subglottic stenosis (33).

- **Rigid endoscopy:**

Under spontaneous ventilation anaesthesia, direct microlaryngoscopy and bronchoscopy provide the most crucial information regarding laryngeal pathology. Because no single type of laryngoscope is appropriate for all cases, a diverse array of instruments should be available. Anterior

or posterior glottic webs, glottic scar tissue, and passive arytenoid mobility, inter-arytenoid adhesions, as well as immobilisation or paralysis of one or both voice cords should be evaluated during the assessment (34).

If the subglottis is patent, the best way to evaluate it is with an appropriately sized Hopkins rod telescope, determining the location (anterior, posterior, and circumferential), age, length, and consistency of the stenosis. Some obstructing factors including collapse, granuloma, fibrous tissue can be found. Also classification of stenotic region should be done. **(35).**

There are 3 classification of subglottic stenosis: Myer Cotton classification system **(36)**, McCaffrey system **(37)** and Lano-Netterville classification **(38)**

According to **Myer et al (36)** ,there are four grades for subglottic stenosis Grade I from 0 to 50%, Grade II from 51% to 70%, Grade III from 71% to 99% and Grade IV No detectable lumen.**(Figure 3).**

Classification	From	To	Endoscopic appearance
Grade I	No Obstruction	50% Obstruction	
Grade II	51%	70%	
Grade III	71%	99%	
Grade IV	No detectable lumen		

Figure (3): Myer Cotton classification **(32).**

According to **McCaffrey system (37),** there are four stages for SGS **stage 1:** less than 1 cm long lesions that are restricted to the subglottis or trachea; stage 2 lesions that are longer than 1 cm and are contained inside the cricoid ring but do not extend to the subglottis or trachea; stage 3 lesions that extend into the upper trachea but do not include the subglottis; and stage 4: Lesion involving the glottis with fixations or para. According to **Lano et al (38),**there are three stages for subglottic stenosis. stage I: one subsite is involved (glottis or sub glottis or trachea). Stage II:two subsites are involved (glottis and sub glottis or subglottis and trachea) .StageIII:three subsite are involved (glottis and sub glottis and trachea).

Pulmonary function tests:

The isolated subglottic stenosis model after endoscopic dilatation exhibits a significant shift in PEF (peak expiratory flow), PIF (peak inspiratory flow), FEV1 (forced expiratory volume in 1 second)/PEF (peak expiratory flow), and FIF (forced inspiratory flow). Postoperatively, the rate of change in PEF and FEV1/PEF is linear, but patient-specific. PIF and FIF50% also alter when re-stenosis occurs, but the lack of standardised methods makes it harder to anticipate the pace of change (39).

In individuals with severe stenosis, the flow-volume loop demonstrates a fixed occlusion of the upper airway. This finding is connected to a decrease in maximal voluntary breathing despite preserving patient effort and muscular strength (40).

Conclusion:

LTS is a heterogeneous collection of disorders with largely unknown causes. Despite the availability of despite advanced endoscopic and open surgical treatments, the illness's inflammatory nature precludes many patients from obtaining complete disease remission. The potentially deadly nature of LTS needs ongoing study into the underlying biological pathways as well as potential adjuvant medicinal interventions to prolong disease-free survival.

References:

1. **Hillel AT, Tang SS, Carlos C et al.** Laryngotracheal microbiota in adult laryngotracheal stenosis.2019.mSphere4: e00211- 9.https://doi.org/10.1128/ mSphereDirect.00211-19.
2. **Gadkaree SK, Pandian V, Best S et al.** Laryngotracheal Stenosis: Risk Factors for Tracheostomy Dependence and Dilation Interval. Otolaryngol – Head Neck Surg. 2016.doi: 10.1177/0194599816675323.
3. **Chen, J. C., & Holinger, L. D.** Congenital laryngeal lesions: pathology study using serial macrosections and review of the literature. Pediatric Pathology, 1994.14(2), 301-325.
4. **Donahoe L & Keshavjee S.** Contemporary management of idiopathic laryngotracheal stenosis. *Thoracic surgery clinics*,2018. *28*(2), 167-175
5. **Maldonado F, Loiselle A, Depew ZS et al.** Idiopathic subglottic stenosis: An evolving therapeutic algorithm. *Laryngoscope*.2014. 124:498-503.
6. **Wang H, Wright CD, Wain JC, et al.** Idiopathic subglottic stenosis: factors affecting outcome after single-stage repair. Ann Thorac Surg. (2015) 100:1804–11. doi: 10.1016/j.athoracsur.2015.05.079.
7. **Shabani S, Hoffman MR, Brand WT et al.** Endoscopic management of idiopathic subglottic stenosis: factors affecting inter-dilation interval. *Annals of otology, rhinology & laryngology*,2016. 126, 96-102.
8. **Veder LL, Joosten KFM, Schlink K, et al.** Post-extubation stridor after prolonged intubation in the pediatric intensive care unit (PICU): a prospective observational cohort study. Eur Arch Oto-Rhino-Laryngol. (2020) 277:1725–31. doi: 10.1007/s00405-020-05877-0.

9. **Hillel AT, Samad I, Ma G et al.** Dysregulated Macrophages Are Present in Bleomycin-Induced Murine Laryngotracheal Stenosis. Otolaryngol – Head Neck Surg;2015. 153(2):244–250. DOI: 10.1177/0194599815589106 [PubMed: 26084828.
10. **Gelbard A, Francis DO, Sandulache VC et al.** Causes and consequences of adult laryngotracheal stenosis. Laryngoscope;2015. 125:1137–1143.
11. **Grillo HC, Mark EJ, Mathisen DJ et al.** Idiopathic laryngotracheal stenosis and its management. *The Annals of thoracic surgery*, 1993.*56*(1), 80-87
12. **Almouhawis HA, Leao JC, Fedele S, et al.** Wegener's granulomatosis: a review of clinical features and an update in diagnosis and treatment. J Oral Pathol Med. 2013;42:507–16.
13. **Dablanca M, Maeso A, Méndez DDC, et al.** Laryngotracheal stenosis of autoimmune aetiology. Acta Otorrinolaringol Esp. 2017;68:38– 2.
14. **Nair S, Nilakantan A, Sood A et al.** Challenges in the management of laryngeal stenosis. *Indian journal of otolaryngology and head & neck surgery*, 2016.68, 294-299.
15. **Valdez TA, Shapshay SM.** Idiopathic subglottic stenosis revisited. Ann Otol Rhinol Laryngol.2002. 111(8):690–695.
16. **Esteller-more E, Ibanez J, Matino E et al.** Prognostic factors in laryngotracheal injury following intubation and/or tracheotomy in ICU patients. *Eur Arch Otorhinolaryngol,2005.* 262, 880-3.
17. **Sandhu GS, Nouraei RS.** Laryngeal and Tracheobronchial Stenosis. *Plural Publishing*,2016. 13-26.
18. **Gelbard A, Katsantonis N-G, Mizuta M et al.** Molecular analysis of idiopathic subglottic stenosis for Mycobacterium species: iSGS Is Associated With Mtb. The Laryngoscope.2016. doi: 10.1002/lary.26097.
19. **Haft S, Lee JY, Ghosh A et al.** Inflammatory Protein Expression in Human Subglottic Stenosis Tissue Mirrors That in a Murine Model. *Ann Otol Rhinol Laryngol.* 2014.123(1):65–70.
20. **Chweiger, Cláudia et al.** Post-intubation acute laryngeal injuries in infants and children: A new classification system. *International journal of pediatric otorhinolaryngology*,2016. 86: 177-182
21. **Cotton, Robin T.** Management of subglottic stenosis. *Otolaryngologic Clinics of North America*,2000. 33.1: 111-130
22. **Agrawal A, Baird BJ, Madariaga MLL et al.** Multi-disciplinary management of patients with benign airway strictures: A review. *Respiratory Medicine*,2021. *187*, 106582
23. **Aravena, Carlos et al.** Idiopathic subglottic stenosis: a review. *Journal of thoracic disease.*2020.
24. **Elderee, Aya et al.** ENT Manifestations in Systemic and Inflammatory Diseases. In: *Textbook of Clinical Otolaryngology.* Springer, Cham,2021. p. 615-623
25. **Bourdillon AT, Hajek MA, Wride M et al.** Correlations of Radiographic and Endoscopic Observations in Subglottic Stenosis. *Annals of Otology, Rhinology & Laryngology*,2021. 00034894211042768
26. **Quinn, Kaitlin A et al.** Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. *Rheumatology*,2019. 58.12: 2203-2211

27. **Fiorelli, Alfonso et al.** Three-dimensional (3D) printed model to plan the endoscopic treatment of upper airway stenosis. *Journal of bronchology & interventional pulmonology*, 2018.25.4: 349-354.
28. **Hoetzenecker, Konrad et al.** 3D models in the diagnosis of subglottic airway stenosis. *The Annals of thoracic surgery*,2019. 107.6: 1860-1865.
29. **Henes, Frank O et al.** Accuracy of magnetic resonance imaging for grading of subglottic stenosis in patients with granulomatosis with polyangiitis: correlation with pulmonary function tests and laryngoscopy. *Arthritis care & research*, 2018.
30. **Dion, Gregory R et al.** Differing progression to posterior glottic stenosis in autoimmune and idiopathic subglottic stenosis. *The Laryngoscope*, 2021.131.8: 1816-1820
31. **Phua CQ, LOH Sh RH, TOH ST.** Selecting Different Surgical Approaches for Hypopharyngeal Obstruction.2019.
32. **Filauro M, Mazzola F, Missale F et al.** Endoscopic preoperative assessment, classification of stenosis, decision-making. *Frontiers in pediatrics*,2020. *7*, 532
33. **Azizollah AD, Mohammad BSh, Kambiz Sh.** Idiopathic subglottic tracheal stenosis in identical twin sisters: Iranian journal of otorhinolaryngology.2019.31(105): 243245. DOI: 10.22038 /ijorl. 2018. 31113.2061.
34. **Muntz H, Morales, Constanza B.** Assessment of the Airway with Rigid Endoscopy. In: Pediatric Respiratory Diseases. Springer, Cham, 2020.p. 161-167.
35. **Rutter, Michael, et al.** Predicting and managing the development of subglottic stenosis following intubation in children. Jornal de pediatria, 2020.96: 01-03.
36. **Myer CM, O'connor DM, Cotton RT.** Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Rhinol Laryngol. 1994.103:319-23.
37. **McCaffrey TV.** Classification of laryngotracheal stenosis. Laryngoscope 1992;102:1335-40.
38. **Lano CF, Duncavage JA, Reinisch L, et al.** Laryngotracheal reconstruction in the adult: a ten year experience. Ann OtolRhinolLaryngol,1998. 107, 92-7.
39. **Kraft, Shannon M et al.** Using pulmonary function data to assess outcomes in the endoscopic management of subglottic stenosis. *Annals of Otology, Rhinology & Laryngology*, 2015.124.2: 137-142.
40. **Elizur A, Goldberg MR, Disin A et al.** A 14-year-old female with fixed airflow obstruction. *Am J Respir Crit Care Med, 2013*.188:1365. 10.1164/rccm.201305-0834IM.