Stenoses of the respiratory tract from the larynx to the bronchi are severe and potentially life-threatening disease manifestations of granulomatosis with polyangiitis (Wegener’s) (GPA). The fundamentals are given in two recent reviews [1,2] with specific sections dedicated to subglottic stenosis (SGS) in vasculitis/GPA. However, the true nature of these stenosing conditions is obscure, hampering the therapeutic access to a cure.

Etiology

The subglottic area represents the junction of two embryological buds, but this does not readily explain the pathological process. The subglottic area is also the site for development of acute laryngitis in children (pseudo croup) usually caused by parainfluenza virus type 1. This would suggest a primary viral infection of this tissue as the initial event, but this has not been documented. Gastroesophageal reflux does not appear to be responsible for SGS [3] as originally proposed in 1985 [4].

Clinical presentation

There are two characteristic variants of SGS: the acute, initial and the late chronic. The acute, initial variant may involve the vocal folds causing hoarseness in addition to stridor (figure 1a). The macroscopic appearance is like the acute, initial lesion in the nose, responding within weeks to traditional corticosteroid treatment (figure 1b). The late chronic variant may be detected in relation to an exacerbation, but has probably been on its way for some time, as this variant appears to have its own life, usually being detected in patients without signs of vasculitic activity. This phenomenon has been referred to as “compartmentalized disease activity” [5]. The late chronic variant usually has a pale, smooth surface (figure 2a), starts 1 or 2 cms below the glottis and biopsies frequently only reveal small bits of scar tissue. This finding could be due to that the initial lesion may cause coughing but not hoarseness or stridor, whereas we observe the chronic fibrotic reaction weeks or months later when stridor brings the patient to our attention. As ¼ of patients with SGS also develop stenoses further down the trachea and the bronchial tree, stridor may not only reflect SGS.

SGS is seen more frequently in young women and has a widely variable course. A few patients only have one episode of SGS whereas another few may have relapses every second month.

Detection

In a recent cross-sectional, systematic study, we found 22% of 121 GPA patients to suffer from SGS, identified by flexible nasolaryngoscopy [6]. This prevalence is in the high end (not including small, selected series from ENT departments treating SGS [7]), probably reflecting that non-symptomatic patients and some patients with stridor/breathing difficulties are not identified as having SGS without sufficient visualization. Even so, flexible nasolaryngoscopy may not always yield a sufficient view of the trachea. Standard X-ray examination of the thorax may not be sufficient either, as the subglottic area may not be included – or the SGS may be misinterpreted to represent the glottis or vice versa. CT-scans – especially with reconstructions of the trachea and bronchi – are better suited but deliver...
radiation. Frequent MRI-scans – although currently still expensive – done routinely could solve the problem, detect additional tracheobronchial stenoses and explore the character and development of the SGS lesion using edema sensitive sequences [8].

**Local treatments**

Recognizing that SGS frequently develops despite optimal systemic therapy and/or while the disease appears to be in remission, several local treatments have evolved over time. When comparing results of various treatment modalities, it must be considered that SGS is relatively rare yielding small study populations and that differences in the composition of the patient materials regarding acute versus chronic lesions, no scarring from previous procedures versus established scarring and frequently versus infrequently relapsing patients are decisive for the results.
Tracheostomy
This treatment, involving a permanent condition with a tracheostomy tube of silver or artificial material to secure patency of the tracheostoma, was the simple solution to the problem until the 1980s [9]. It may still be relevant for emergency situations and for rare cases with severe destruction of the laryngeal and/or tracheal structures securing a patent airway, but with the description of the beneficial effect of intratracheal dilation and glucocorticoid injection therapy in 1996 [10], most tracheostomies have been closed and not later considered relevant.

Dilation/dilatation
All sorts of procedures have been used – apparently with more or less the same favourable response. The originally described procedure [10,11] used serial dilation with bougie dilators and this procedure is still used successfully [12]. However, as these dilators are solid, this procedure requires intermittent apnea. This can be avoided by using a laser tracheoscope with a diameter increasing slightly from the tip to the handle. By gently but firmly passing the tracheoscope through the SGS, this is dilated, and the patient can be ventilated during the 15 minutes, the tracheoscope is left in place. This procedure also allows for additional CO2-laser treatment if desired [12]. The tracheoscope dilation principle has been further refined by the development of the Groningen Dilation Tracheoscope [13,14], which appears to be just as effective as the bougie dilations. The dilation can also be performed using a balloon like the Fogarty catheter balloon [11]. This procedure also requires intermittent apnea when used in the trachea. With the fast technological evolution of balloon dilatation, this alternative has become more attractive, especially in more severe cases with additional tracheobronchial stenoses [15–17]. However, in contrast to the SGS, where the cricoid cartilage provides a framework to keep the subglottic space patent, the trachea and bronchi only have semicircular cartilage support, and if these cartilages are damaged, dilation will not be sufficient in a longer perspective [15]. In such cases, stenting or surgical reconstruction will be required.

Stenting
For tracheal collapse, a T-tube of silicone is appropriate, as this can be tailored to the tracheal pathology, and possible crusts or viscous secretions can be removed through the part of the tube passing from the trachea through the skin just below the larynx. This “outlet” tube is usually closed by a simple silicone cork, permitting the patient to breathe normally through the mouth and speak without having manually to close the “outlet”, as is frequently necessary if a standard tracheostomy tube is used. In some cases with distal tracheal stenoses and/or additional bronchial stenoses, stenting using the fast developing technologies applied for vascular stenting have gained access to the airways. With the advent of highly flexible and removable stents, prior problems of stenting with formation of granulation tissue, displacement and perforating of the airway wall [18] are presumably diminished.

Surgical reconstruction
This follows the principles for managing post-intubation tracheal stenosis and includes resections of the stenosis and end-to-end anastomosis of the trachea [19]. In contrast to the post-intubation related lesions, SGS in GPA patients may still relapse, which eventually will limit the possibility to perform further restenoses of the trachea.

Laser treatment
Prior to the introduction of dilation, lasers – mainly CO2-lasers – were used to remove the stenoses with variable results [20,21]. A major reason for less favourable results is that laser evaporation/tissue excision leaves an open wound. Circumferential lesions like most SGS will therefore tend to re-stenose and even progress as they heal, unless microflaps are raised to cover the wounds as originally [22] and recently [23] described. The open wound problem may to some extent be prevented by only performing radial incisions, which may be effective for short, shelf-like stenoses, but with larger stenoses a combination with dilation is required. The radial incisions, however, can also be performed with microlaryngeal scissors or knives as originally described [11,12].

Intralesional corticosteroid injection
This treatment was introduced to combat disease on site, as systemic treatment appeared ineffective [10]. The intralesional injection given after dilation is aiming at preventing scarring and restenosis. It is frequently – especially in the late, chronic type – difficult to inject any material in the stenotic tissue and the material may leak out as also described originally [10]. An alternative is postoperative inhalation of glucocorticoids for a month (like in severe asthma) as the inhalation procedure may result in subglottic deposition of clococorticoid due to turbulence. In both cases, the local treatment is supported by systemic bolus methylprednisolone injections at the operation. The effect of local glucocorticoid treatment may therefore be limited and it was not found to be effective in one study [24].

Mitomycin-C
The same study [24], however, found a significant effect of the use of mitomycin-C, supported by a randomized clinical trial showing that two applications of mitomycin-C is better than one application on a 2-year basis, but is not effective on a 5-year basis [25]. Animal studies on the other hand find application of mitomycin-C to be potentially dangerous due to crust formation [26] which has also recently been reported in patients where no positive effect of mitomycin-C was observed [17]. As stated in the reviews [1,2], the role of mitomycin-C is therefore still open for discussion.

Monitoration
In order to evaluate the results of local treatment, it has been difficult to define the best surrogate endpoints due to the wide
variability in relapse rate. So far, the number of required interventions over a given time and the corresponding intervals between treatments have been used. Video laryngoscopy, as illustrated in figures 1 and 2, is well suited to document treatment effect, and imaging – especially 3D reconstructions – yields precise spatial information. Other options are the use of serial peak-flow measurements, which can be performed frequently by the patients [13], or the use of flow-volume curves [21] or other pulmonary functional tests [15].

**Conclusion**

This review describes the many local treatment modalities and combinations of these. Due to the usually small and selected patient populations, the results may be difficult to compare. However, most authors, irrespective of treatment modality, find an average of three interventions per patient to be necessary. This calls for multi-center randomized clinical trials based on harmonized criteria for diagnosis, type of SGS and monitoring of treatment results in order to substantiate the effect of any single treatment modality and improve the outcome of local treatment.

**Disclosure of interest:** the author declares that he has no conflicts of interest concerning this article.

**References**


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