

Clinical characteristics and treatment of subglottic stenosis in patients with Wegener's granulomatosis

Subglottic stenosis is a complication of Wegener's granulomatosis caused by tracheal tissue damage and scarring. It may occur as a presenting feature of the disease leading to diagnosis, or instead as a late-stage manifestation. Frequently, it occurs or progresses independently of other features of active disease, and sometimes appears while the general disease is in remission under therapy. The diagnosis of isolated subglottic stenosis may be difficult histologically. Thus, a combination of clinical, histopathological and immunological tests is needed to establish the diagnosis. The management of subglottic stenosis is challenging. A subset of patients may not be responsive to immunosuppressant medication and fixed lesions may require surgical repair. An individualized approach that may include medical and interventional therapies is recommended.

KEYWORDS: interventional procedure ■ subglottic stenosis ■ tracheal stenosis
■ virtual bronchoscopy ■ Wegener's granulomatosis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the diagnosis and prognosis of Wegener's granulomatosis
- Diagnose SGS in the setting of Wegener's granulomatosis effectively
- Devise a treatment strategy that is responsive to the disease course of SGS in Wegener's granulomatosis

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Systemic vasculitides are a heterogeneous group of uncommon diseases characterized by inflammatory cell infiltration and necrosis of blood vessel walls. These conditions often have overlapping clinical and pathological manifestations that sometimes make it difficult to reach a precise diagnosis. Vasculitides are classified according to the size of vessel predominantly involved and the histological appearance on biopsy [1,2]. Wegener's granulomatosis (WG), Churg–Strauss syndrome and microscopic polyangiitis are the paradigm of vasculitis involving small vessels and medium arteries and are associated with the presence of circulating antineutrophil cytoplasmic autoantibodies (ANCA) [3]. They are chronic and relapsing diseases, which may have serious consequences if not recognized and treated promptly.

Wegener's granulomatosis is a multisystem disease with a clinical predilection for involvement of the upper airways, lungs and kidneys [4,5]. Histologically, it is characterized by foci of necrotizing vasculitis and granuloma formation. Otolaryngological manifestations such as chronic nasal discharge, paranasal sinus disease, middle ear inflammation and sensorineural hearing loss occurs in approximately 80–90% of patients with WG at some point of disease evolution [4–8], but tracheobronchial involvement is a less common complication [6–11].

Wegener's granulomatosis is classified as a severe or generalized disease, and limited or localized disease. Limited disease, in contrast to severe disease, includes manifestations of WG that pose no immediate threat to either the patient's life or the function of a vital organ [4,7,12,13]. In terms of the current standard of care, the distinction between limited and severe disease subsets is important because it has practical implications for treatment. Severe disease requires prompt initiation of an aggressive therapeutic regimen that includes cyclophosphamide and glucocorticoids. By contrast, limited disease usually responds well to a less toxic alternative regimen consisting of methotrexate and glucocorticoids [4,14].

Current therapies have transformed WG from a fatal disease into a chronic condition in which most patients achieve remissions, some of which last for several years. However, disease flares following the tapering or discontinuation of treatment are frequent and treatment-induced side effects are a major source of morbidity and mortality [4,7]. Repeated relapses of the disease can lead to permanent damage and usually do not respond to immunosuppressive therapy [15].

Subglottic involvement in vasculitis

The immediate subglottic region of the trachea is well-known to be particularly susceptible to narrowing. Several contributing factors, such as the exposure of respiratory epithelium to gastric contents, a tenuous blood supply located at the junction of two separated microvascular beds, complex mechanical forces related to turbulent subglottic airflow and the complete ring that comprises the cricoid cartilage, have been described.

Subglottic stenosis (SGS), that is, narrowing of the upper airway at the level of cricoid cartilage and/or upper tracheal rings, is a well-known potentially life-threatening presentation of WG that may occur either as a presenting feature or as a late-stage symptom of the disease [9,11].

Clinical characteristics of subglottic stenosis

Subglottic stenosis with circumferential scarring and critical narrowing of the airway appears in 10–16% of WG patients at some time during the course of the disease [4–6,9,11]. However, only about 2% of patients are initially seen with this manifestation [8–11]. Usually, the constricting lesion progresses slowly and the patients are able to adjust their breathing pattern gradually, until a critical point of stenosis is reached. Symptoms range from cough and shortness of breath to life-threatening dyspnea with stridor [9,11]. According to the NIH experience, half of the patients need a tracheostomy at the moment of diagnosis [16]. SGS appears to be more frequent in childhood-onset WG than in adult-onset disease [17].

Based on the form of presentation of SGS, two general groups of patients have been distinguished [10,11]. The first group consists of patients who present with isolated SGS with no organ involvement outside of this region. The patient's main complaints are dyspnea on exertion, cough and stridor. Sometimes, these patients had previously experienced other otolaryngological manifestations such as nasal, paranasal or middle ear disease that had been misdiagnosed. Sometimes, SGS appears in association with chronic nontreated otolaryngological manifestations [10,11], and occasionally SGS appears alone as a limited form of the disease. Often, patients with SGS had been unsuccessfully treated for presumed asthma, with further evaluations suggesting tracheal involvement. With the increasing use of ANCA as a diagnostic tool, WG is now diagnosed earlier than in the past and not infrequently when only ear, nose and throat manifestations are present [18].

The second group consists of patients with a known diagnosis of WG who then develop symptoms of SGS. In the vast majority of cases, symptoms of SGS arise in the absence of signs indicating active WG [10]. Subglottic lesion may appear following the tapering or discontinuation of treatment, or after a prolonged period of remission. In both cases, a local flare of SGS may not reflect generalized disease activity [9,11].

Diagnosis of subglottic stenosis

Since SGS has nonspecific symptoms such as progressive shortness of breath, hoarseness, cough, stridor or wheezing, a high index of suspicion is important in its detection, especially if no other features of active WG are present. All these manifestations may be mimicked by other diseases and stridor can easily be misdiagnosed as the wheeze of bronchial asthma [19].

Given the life-threatening potential of SGS, all patients in whom SGS is being considered should be evaluated by an otolaryngologist immediately [9,16,18].

The diagnosis should be made by the demonstration of vasculitis, granulomatous inflammation and necrosis in a clinical setting. However, these histological features are often inconsistent and a negative biopsy does not necessarily exclude the diagnosis [9–11]. For this reason, nasal and paranasal sinus involvement should be ruled out in all patients with suspected WG. Granulomatous inflammation of the nose and paranasal sinuses is an excellent target for representative biopsies, even if in the chronic stages of the disease the sinus may become filled with scar tissue and CT/MRI scans are not capable of making a distinction between granulomatous inflammation and residual damage.

Once WG-related SGS has been diagnosed, patients must be monitored closely for signs of airway compromise. The severity of stenosis may be carefully determined by endoscopic examination, radiological measurement of the length of the stenotic segment and flow–volume loop studies [9,11].

Diagnostic procedures

■ Indirect or fiberoptic laryngoscopy

This is a noninvasive technique that should always be performed by an experienced otolaryngologist when SGS is suspected, although it usually does not show the entire trachea [18].

■ Fiberoptic bronchoscopy

This enables the assessment of the severity of luminal airway narrowing and to establish the

diagnosis by biopsy. However, the degree of stenosis sometimes prevents further passage of the bronchoscope to the distal trachea, so the length of the obstruction is not measurable. This fact is important because the extent of stenosis influences the choice of therapy, less invasive modalities being indicated for shorter obstructions. The visual appearance of the laryngeal mucosa at endoscopic examination may help to determine whether lesions are due to active inflammation or scar tissue, even though visual changes do not always correlate with histological findings [9]. Macroscopically, inflammatory lesions usually appear as a reddish, friable, circumferential narrowing just below the vocal cords, irregular granulomatous formations partially obstructing the airway, or inflammatory ulcers.

■ Histopathology

Biopsy of the stenotic area must always be performed, even though examination from the upper respiratory tract is difficult and most biopsies fail to demonstrate the diagnostic features of WG, such as small vessel vasculitis, epithelioid granulomas and fibrinoid necrosis, and only reveal chronic inflammation and fibrosis [9,10]. Consequently, multiple biopsies of inflamed areas are recommended.

Imaging tests

■ MRI & tracheal tomography

These are useful diagnostic tools that can aid in the planning of bronchoscopy or therapeutic intervention, but should not be used as primary means of diagnosis because they are insensitive means of viewing the lesion and may lead to an unacceptable delay in diagnosis [20]. The diseased portions of the trachea typically have circumferential mucosal thickening, irregularity and ulceration (FIGURE 1). Irregular formations partially obstructing the airway may also be visualized. Involvement of the cartilaginous rings is less common, but may result in deformity and narrowing of the trachea.

Spiral CT-scan with 3D reconstruction (3D-CT) of the laryngotracheal lumen and virtual bronchoscopy provides complementary information to bronchoscopy and allows more accurate definition of the length and severity of the stenotic area, the upper and lower limits of lesion, and the status of airway distal to obstruction (FIGURES 2 & 3). This technique is especially useful for treatment planning, evaluating response to treatment and assessment of the airway patency during the follow-up [21–23]. Unstable stenoses demonstrating evidence of progression over time could motivate referral

for interventional bronchoscopy [22]. However, virtual bronchoscopy has several intrinsic limitations, such as the inability to perform biopsies for histological assessment and the inability to distinguish between residual damage and active disease. Conventional endoscopy therefore remains the gold standard for the identification and characterization of airway lesions of any size and virtual bronchoscopy should be regarded as a complementary technique.

Pulmonary function tests

Pulmonary function tests are useful not only for objective assessment of respiratory symptom, but also for estimation of disease response to therapy. The presence of SGS may be suggested by flattening of the inspiratory curve on flow-volume loop measurement, which is diagnostic of an extrathoracic airway obstruction. However, nonsevere SGS may not be detected by this technique and for this reason it should never be used as the primary means of diagnosis [9,24].

■ Biomarkers

Antineutrophil cytoplasmic autoantibodies with PR3 specificity (C-ANCA) may confirm the diagnosis since these are specific markers for WG

with rare false-positive results [9,10]. However, a negative result does not rule out WG diagnosis because only 60% of patients with localized WG show positive ANCA [4,5]. This test should not normally be used in place of a biopsy sample to make the diagnosis, but given the difficulty in the examination of biopsies from the upper respiratory tract [19], a strongly positive C-ANCA/PR3-ANCA may be considered to confirm the diagnosis.

■ Differential diagnosis

Other causes of SGS (e.g., postintubation stenosis, postracheostomy cicatricial stenosis, tracheal rupture, extrinsic compression by thyroid neoplasms and goiters, congenital stenosis, gastric reflux, infections, inflammatory conditions, benign or malignant neoplasms, and idiopathic progressive SGS) should be excluded because their optimal treatments differ considerably and delay contributes to increased morbidity and mortality [16,18,25]. Congenital stenosis typically presents at young age and is often the result of posterior fusion of the tracheal rings, thereby forming complete rings. Primary benign tumors of the trachea, such as chondromas, fibromas, papillomas, hemangiomas and granular cell tumors, are rare causes of stenosis. Tuberculosis and fungal infections such as histoplasmosis and balstomycosis should always be considered when the etiology of SGS is not clear, especially in patients receiving immunosuppression therapy. Serologic testing and histopathologic examination can be helpful in this regard. Noninfectious, inflammatory causes of SGS (e.g., relapsing polychondritis, primary amyloidosis and sarcoidosis) may be ruled out by clinical evaluation and histopathologic examination [25].

Treatment of subglottic stenosis

The optimum treatment of SGS is challenging [8,9]. Both surgical and medical treatments have been used, but the optimal therapeutic approach has not been determined. Subglottic lesions are not universally responsive to conventional systemic therapy and aggressive treatment may favor fibrosis development [9,16,26–28]. Therefore, systemic agents may not be primarily indicated in isolated SGS and interventional procedures should be considered.

Treatments of SGS may differ not only depending on the presence of major organ involvement, but also on the type of stenosis [16]. If the stenosis is short and due to active disease it may be managed by standard medical treatment. By contrast, when scarring lesions are present due to tissue destruction from a previously active disease,

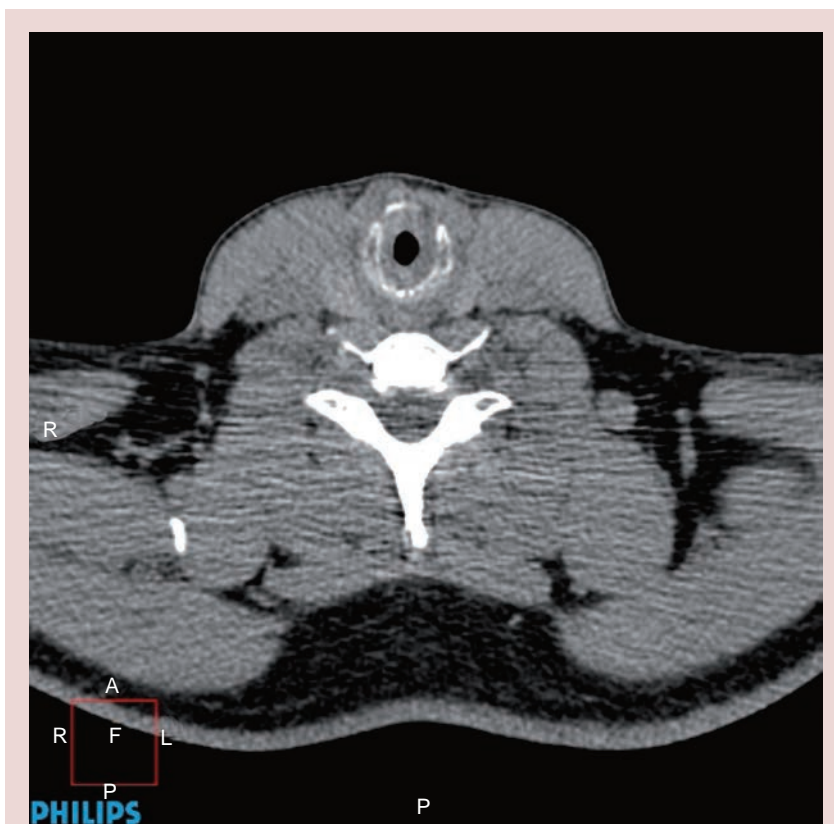


Figure 1. CT tracheal scan showing circumferential mucosal thickening.

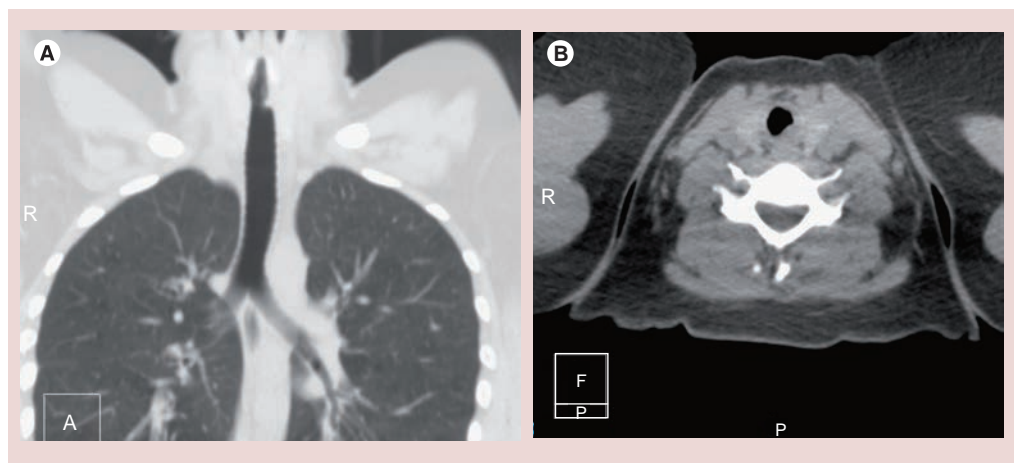


Figure 2. 3D images based on computed tomography data. Coronal (A) and axial (B) view, showing irregularity and mild asymmetric stenosis at the level of the subglottis and upper trachea.

special interventions used alone or in combination with conventional treatment may be needed to avoid a chronic tracheostomy. The patient's symptoms including the general health, the activity of the disease and the severity of SGS all determine the management plan. Despite all therapeutic attempts, tracheotomy may be necessary in particularly difficult cases of SGS [9,10,11,16,29].

■ Immunosuppressant drugs

Glucocorticoids in combination with an immunosuppressive agent have markedly decreased the mortality and morbidity rates from active WG that affects major organ systems [4,5,7]. This therapy has also been successfully employed to treat patients with WG-related SGS [30]. However, subglottic lesions do not always respond to systemic agents and approximately 75% of patients may require interventional therapies to improve their symptoms [9,16,26,27]. In addition, local relapses of the disease are frequent after treatment tapering or discontinuation, and supplementary courses of therapy are needed, thereby increasing the risk of treatment-related toxicity, including fibrosis development [9,16,26,27,28]. The rationale for avoiding immunosuppressive therapy in the management of SGS is also supported by the frequent development of SGS in patients receiving systemic treatment for other WG manifestations [9,11]. For all these reasons, the use of single systemic agents in the treatment of subglottic lesions is questionable and interventional procedures alone or in combination with conventional therapy may be considered [9,10,16,26–28,31–36].

■ Interventional procedures

Interventional procedures consist of endoscopic tracheal dilation, conservative endoscopic surgery, laser therapy, stenting and surgical

resection of the stenotic segment followed by reconstruction [9,10,16,26–28,31–36].

Endoscopic dilation with a rigid bronchoscope or tracheoscope is a minimally invasive technique that can be used for elective and emergency intervention [26]. It requires short hospitalization and is not stressful for the patient. The intervention can be repeated if necessary after any time interval. No antibiotics or corticosteroids are used and complications are rare.

According to the technique described by Langford *et al.*, intratracheal dilation injection therapy, also named intralesional long-acting corticosteroid injection and dilation (ILCD), provides a safe and effective treatment for WG-associated SGS and in the absence of major organ disease activity, may be used without concomitant systemic immunosuppressive agents [9]. ILCD has been recommended as the preferred therapy for SGS [29], although there have been no large controlled trials. Corticosteroid injections have been shown to diminish inflammation and to impair both fibroblast production of collagen and scar formation. Mechanical dilation disrupts scar tissue that may be present in these lesions. These combined mechanisms of action explain why this technique may be an effective treatment in treating all types of WG-related subglottic lesions regardless of whether they are inflamed or scarred. This procedure minimizes the treatment-related toxicity by avoiding supplemental immunosuppressant drugs and allows patients to achieve extended periods of airway patency. Laryngotracheomalacia from repeated steroid injection causing airway collapse has not been described.

Mitomycin C, an alkylating agent that inhibits fibroblast proliferation and extracellular matrix protein synthesis [37], has been increasingly used

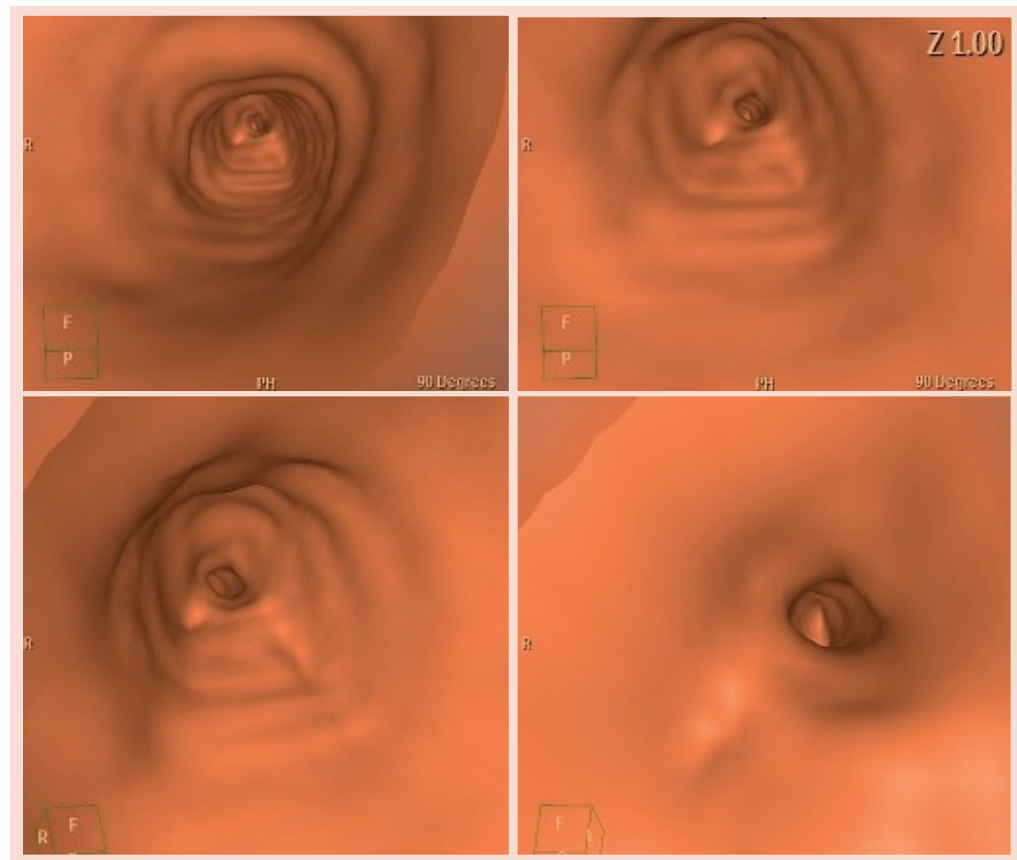


Figure 3. Virtual bronchoscopy showing concentric stenosis.

topically as adjuvant treatment in selected cases of tracheal stenosis in patients with WG following ILCD [10,27,29] or laser surgery and dilation [35,37,38], with the intent of reducing fibrosis and re-stenoses. However, a randomized, double-blind, placebo-controlled trial of patients with laryngotracheal stenosis that compared the re-stenoses rates after repeated applications of mitomycin C failed to demonstrate long-term advantages [38]. Some authors recommend its use only in patients with active inflammatory lesions [26].

■ Conservative endoscopic surgery

Endoscopic removal of the granulomatous tissue by conventional or laser surgery is an effective strategy for treating airway compromise due to active tracheal WG, obviating the need for airway bypass or stenting. It can be performed alone or in combination with tracheal dilation [35,39].

Laser therapy with carbon dioxide or Nd:YAG lasers has been employed in patients with SGS secondary to WG with different results [10,16,32]. Some authors reported good results after repeated sessions of both lasers [10,32], but other investigators described rapid restenosis

after treatment [16]. It is recommended to avoid laser therapy during periods of disease activity [10]. Better results may be obtained when the stenosis is short [16]. Lasers may produce extensive thermal necrosis and damage subglottic mucosa, leading to an extensive fibroblastic response [29,40]. Subsequently, scarring and cicatrix formation after laser therapy has been reported [16,40].

■ Stenting

There are few studies dealing with the treatment of SGS with stents and the results are discordant [16,24,41,42]. Silicone stents are preferred because metal stents can only be removed with great difficulty and may also penetrate to the adjacent tissue. Caution is advised due to the potential difficulty in performing emergency tracheostomies or intubations [42].

■ Reconstructive surgery

Surgical repair should be reserved for patients with fixed lesions during periods of disease quiescence to avoid recurrence of the disease at the anastomotic site. It is strongly recommended that airway manipulation be minimized in the setting of acute systemic disease activity [10,16].

Ideally, patients will have had systemic steroid therapy minimized before reconstruction. Some authors recommend surgery only in patients who are in remission and have required no immunosuppressive therapy for at least 1 year [27,10]. However, successful tracheal reconstruction has been reported in patients in remission receiving immunosuppressive therapy [34].

Different surgical techniques have been used to treat WG-related SGS with variable success and decannulation rates of approximately 50% caused by continued disease and restenosis [10,16,26,27,33,34]. These techniques may be useful when endoscopic procedures fail [10,16]. Herridge *et al.* reported good results after open laryngotracheal repair of SGS with resection of the stenotic area and primary reanastomosis as a definitive reconstructive procedure [34].

Biological therapies

Attempts to treat systemic vasculitis with new biologic therapies, specifically TNF- α -blocking agents, have not been encouraging [43,44].

The use of infliximab in combination with conventional therapy has been associated with a high rate of infections, including tuberculosis [43]. Treatment with etanercept has also been related to an increased rate of infections and solid malignancies [43].

By contrast, recent studies suggest that B-lymphocyte depletion with the chimeric, monoclonal antibody rituximab directed against CD20⁺ B-cells may be promising [45,46]. Rituximab leads to a swift depletion of circulating B-cells, which become undetectable in the peripheral blood. Subsequently, ANCA production is inhibited and remission of the disease is induced.

The potential benefit of rituximab in treating disease manifestations that are typically not improved by standard immunosuppressive regimens, such as SGS, has also been examined and the evidence seems to suggest that, similar to conventional immunosuppressive therapies, rituximab is less effective in refractory granulomatous disease than in vasculitic phenomena [45-47]. Refractory granulomatous disease represent a subset of patients who are particularly difficult to treat and are likely to be pathogenetically different from the vast majority of patients with WG with predominantly vasculitic manifestations. In this sense, more knowledge is needed about the role of the various elements of the immune system in order to tailor more precisely targeted biological therapies.

■ Trimetoprim-sulfamethoxazole

Although antibiotic treatment cannot cure WG, an additional beneficial action may be obtained by giving trimetoprim-sulfamethoxazole to the patient since it seems that therapy with trimetoprim-sulfamethoxazole can reduce the number of relapses, especially in the ear, nose and throat area [48]. It is possible that a part of the mechanism is a direct effect on *Staphylococcus aureus* because the presence of this microbe is linked to an increased frequency of flares of the disease [49]. Because *S. aureus* may exert direct effects on the immune system through release of superantigens or may play a more direct role by facilitating binding of ANCA to and activation of endothelial cells, modification of the chronic nasal carrier condition appears relevant for disease control.

■ Additional measures

It should be stressed that successful airway maintenance in WG goes beyond providing luminal patency of tubular structures. Clearance of secretions and meticulous care of the sinonasal tract are crucial. Humidification of the home environment, aerosol respiratory therapy, local nasal and sinus hygiene, liquid irrigation for removal of crusts, and lubricating creams and gels may be all helpful.

Prognosis of subglottic stenosis

In general, WG patients do not die from the disease's otorhinolaryngologic manifestations. The exception to this is severe untreated SGS [19]. In patients with known SGS, worsening dyspnea, voice changes or cough should be immediately evaluated by an otolaryngologist. It should be taken into account that not all SGS manifestations will reflect active vasculitis. Certainly, in the later stages of the disease, when the patient has been treated and the remission phase has been reached, more or less residual damage may remain and it may be difficult to distinguish between manifestations due to damage, infection or active disease. Obstruction may occur not only from the subglottic lesion itself, but also from crusted and thickened secretions that can result from mucosal inflammation or intermittent upper or lower respiratory tract infections. In this setting, CT and MRI scans are not capable of distinguish between active disease and infection. Spiral CT virtual bronchoscopy may be useful to visualize the tracheal lumen with the same endoluminal perspective as conventional endoscopy and to demonstrate evidence of progression over time. The presence of C-ANCA or

a rise in C-ANCA titers may suggest a relapse, although rising ANCA titers do not necessarily herald relapse and *vice versa* [50].

Progressive complaints and progressive decline of peak flow values should indicate that an interventional procedure is needed. Fiberoptic bronchoscopy and biopsy may be helpful showing inflammatory changes (vasculitis and/or granulomata) or instead residual scarring tissue.

A carefully follow-up is essential in these patients to prevent fatal complications.

Conclusion

Subglottic stenosis is a life-threatening complication of WG that may be successfully managed by conventional immunosuppressive therapy and mechanical dilation, but the disease tends to relapse and additional immunosuppressive therapy and dilations are needed to again achieve clinical remission. ILCD is a safe alternative to conventional immunosuppressive therapy in patients with known WG who develop SGS in the absence of other features of active disease, allowing a reduction in treatment-related toxicity. Patients who require immunosuppressive treatment for other WG manifestations should undergo ILCD concurrently. Isolated SGS can be effectively managed using ILCD alone. Surgical repair should be reserved for patients with fixed lesions during periods of disease quiescence when endoscopic procedures fail.

Residual damage caused by a cicatricial process is one of the major sources of morbidity in WG patients and is not always easy to distinguish between symptoms due to active disease and symptoms due to remaining damage.

A multidisciplinary and individualized approach to assessment and management of the disease involving thoracic and ear, nose and throat surgeons, respiratory physicians, radiologists and vasculitis specialists is the best strategy for the benefit of the patient.

Future perspective

Modern therapeutic strategies have greatly improved the immediate prognosis of patients with WG, but there is a need to focus on the long-term consequences and consider how to monitor and prevent the damage that results from recurrent flares, chronic low-level disease activity and long-term exposure to glucocorticoids and immunosuppressive therapies. Future studies must focus not only on early identification of subclinical forms of damage, but also on the development of new treatments that minimize the development of damage. Advances in immunology and molecular biology may facilitate the understanding of the disease pathogenesis and improve therapeutic regimens.

A future option for patients with chronic and severe tracheal stenosis may be tracheal transplantation [51,52].

Executive summary

- Subglottic stenosis represents a significant complication and is an important cause of morbidity among patients with Wegener granulomatosis.
- Decisions concerning the need for immunosuppressive therapy should be based upon extratracheal disease activity. Isolated subglottic stenosis can be effectively managed with local therapy and conservative surgery.
- The role of new biologic agents in the treatment of refractory or relapsed subglottic stenosis is unclear.

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1 A 39-year-old woman was diagnosed with Wegener's granulomatosis (WG) last year. She has had limited disease, which has responded well to treatment. Which of the following statements about WG is most accurate?

- A Pathology is confined to the upper airways and lungs
- B Otolaryngologic complications occur in up to 90% of patients
- C Treatment should consist of cyclophosphamide and glucocorticoids, regardless of disease severity
- D WG remains a fatal disease for most patients

2 The patient complains of persistent dry cough and some mild-to-moderate dyspnea. Which of the following statements about the possibility of subglottic stenosis (SGS) is most accurate?

- A SGS appears in 10% or more of WG cases at some point in the course of illness
- B Severe interventions, such as tracheostomy, are extremely rare in cases of SGS related to WG
- C SGS does not occur without other signs of active WG
- D SGS always heralds a generalized flare of WG activity

- 3 Which of the following statements about making the diagnosis of SGS for the patient is most accurate?
- A A biopsy of the stenotic area negative for signs of WG excludes the diagnosis of SGS
 - B Determination of the length of obstruction during the diagnosis of SGS helps guide treatment
 - C MRI and tracheal tomography are considered the primary means of diagnosis of SGS
 - D A negative test for antineutrophil cytoplasmic antibodies (ANCA) effectively rules out the possibility of SGS

- 4 The patient has isolated SGS without signs of active WG. What is the best treatment for her now?
- A Corticosteroids
 - B Infliximab
 - C Intralesional long-acting corticosteroid injection and dilation (ILCD)
 - D Placement of metal tracheal stents