

# Multilevel Airway Involvement in Children With Wegener's Granulomatosis

## Clinical Course and the Utility of a Multidisciplinary Approach

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**Objective:** To examine the prevalence of airway involvement in children with Wegener's granulomatosis (WG) at our institution and to evaluate the utility of a treatment paradigm involving a multidisciplinary team.

**Design:** Retrospective medical chart review.

**Setting:** Tertiary children's hospital.

**Patients:** Pediatric subjects with WG treated at a tertiary children's hospital over the past 15 years.

**Main Outcome Measures:** The medical records of all subjects with airway lesions were reviewed for clinical characteristics of airway involvement and for the medical and surgical treatment regimens.

**Results:** Seven of 28 pediatric patients with WG were identified to have airway lesions (25%), including vocal fold granuloma, subglottic stenosis, and multilevel stenoses. Three of these patients had isolated and limited

lesions. The 4 remaining patients are the focus of this study. One patient underwent a cricotracheal resection. All patients underwent repeated surgical treatment from combined services (otolaryngology and pulmonology) with flexible and rigid endoscopy, dilatation, and corticosteroid injection to manage subglottic, tracheal, and bronchial stenoses. Operative findings were communicated to the rheumatology service for manipulation of medical therapy. The 3 most recent patients received the anti-CD20 chemotherapeutic agent rituximab. This treatment approach led to temporary remission in some of the patients.

**Conclusions:** Airway involvement in pediatric patients with WG is known to occur, but multilevel airway involvement is rare and clinically challenging. We advocate a combined surgical approach involving otolaryngology, pulmonology, and rheumatology in managing aggressive cases of multilevel airway involvement in WG.

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**W**EGENER'S GRANULOMATOSIS (WG) is a necrotizing granulomatous vasculitis primarily affecting the small and medium-sized vessels. Any portion of the body may be involved, but most commonly the upper and lower respiratory tract are affected, with eventual renal involvement. Presenting symptoms are often manifested in the ear, nose, and throat such as sinusitis. In children, there appears to be a female predominance, and patients often present in adolescence with subglottic stenosis causing symptoms of cough and dyspnea.<sup>1-3</sup> The course of the disease tends to be relapsing and remitting, but in untreated instances it can become rapidly fatal.<sup>4</sup>

Conventional treatment for WG involves steroids as well as cyclophosphamide with the occasional addition of methotrexate and/or other immunomodulating drugs. Cyclophosphamide often has limiting adverse effects such as bone-marrow

suppression, alopecia, and hemorrhagic cystitis. Recently, rituximab has been used as an additional treatment in cases refractory to other therapies or in which adverse effects make the treatments intolerable. Rituximab is a monoclonal anti-CD20 chimeric antibody that was originally used to treat B-cell lymphoma. The therapy depletes B cells as well as the antineutrophil cytoplasmic antibodies (ANCA). Previous reports have shown good results in patients treated with rituximab in whom the cytotoxic effects of cyclophosphamide could no longer be tolerated.<sup>5,6</sup>

Surgical interventions are typically reserved for complications from the disease to preserve the airway or prevent progressive infections. Within the tracheobronchial tree, preservation of airway patency and adequate gas exchange are the most important goals. There are limited reports regarding tracheostomy, dilatation, intraleSIONAL steroid injection, pulmonary stenting, and pulmonary resection for the treatment of airway disease.<sup>7-13</sup> Traditionally, these pro-

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**Table 1. Characteristics of All Patients With Airway Lesions and Surgical Interventions Undertaken**

Characteristic	Patient No.						
	1	2	3	4	5	6	7
Age at presentation, y	16	13	8	14	6	16	19
Sex	M	F	F	M	F	F	F
Symptoms at presentation	Arthralgia, hemoptysis	Sinusitis, otitis media	Stridor	Nephritis, arthralgia	Sinusitis	Hoarseness, nephritis, sinusitis	Hemoptysis
Initial presenting airway lesion	Pneumothorax	Subglottic and tracheal stenosis	Subglottic stenosis	Subglottic stenosis, pulmonary granulation	Subglottic stenosis	Vocal cord granuloma	Subglottic stenosis
<b>Surgical Intervention</b>							
Endoscopy	X	X	X	X	X	X	X
Balloon dilatation	X	X	X	X			
Thoracic intervention	X		X				X
Cricotracheal resection	X						
Laser excision and/or dilatation	X	X					
Steroid injection	X	X	X	X			
<b>Medical Intervention</b>							
Corticosteroid	X	X	X	X	na	na	na
Antineoplastic agent	X	X	X	X	na	na	na
Immunomodulator		X			na	na	na
Monoclonal antibody		X	X	X	na	na	na
Plasmapheresis	X		X	X	na	na	na

Abbreviations: na, not applicable; X, named characteristic applies to given patient; blank table cell, named characteristic does not apply to given patient.

cedures may involve otolaryngologists, pulmonologists, or cardiothoracic surgeons as needed, but each operating independently. Our recent experience in managing several complex cases of WG has made us rethink the utility of the traditional method. Hence, we conducted a retrospective review of our institutional experience to examine the prevalence of airway involvement in our WG population and evaluated the utility of a paradigm involving a multidisciplinary team of rheumatology, pulmonology, and otolaryngology to combat progressive airway involvement due to WG with both rituximab and corticosteroids as medical therapy and periodic surgical intervention.

## METHODS

Approval was obtained from the Colorado Multiple Institute Review Board to conduct a retrospective medical chart review for this study. A 15-year retrospective review at The Children's Hospital, Aurora, Colorado, was undertaken to identify children with WG and airway involvement. Records were analyzed for general descriptors such as age at presentation, sex, medical treatment, and surgical intervention. The children requiring surgical intervention by otolaryngology were then placed in a subgroup for further review. These cases are reported herein to describe and evaluate the surgical interventions undertaken by the otolaryngology and pulmonology services in partnership with medical therapy by the rheumatology service in a multidisciplinary approach.

## RESULTS

### DEFINING THE STUDY CASES

Twenty-eight patients were identified from a database encompassing patients who were treated between 1994 and

2009 for pediatric WG our institution. There were 14 boys and 14 girls. The mean age at presentation was 13.0 years (range, 6-19 years).

Of these 28 patients, 7 (25%) had airway lesions at initial presentation categorized as multilevel involvement (4 subjects) or isolated lesions (3 subjects) using a chronological numbering system based on the date of presentation (**Table 1**). The mean age at presentation for subjects with airway involvement was 12.7 years (range, 6-19 years). No age difference was found between the 2 subgroups. Isolated airway lesions included 1 with vocal fold granuloma and 2 with subglottic stenosis. Two of these subjects (patients 5 and 6) did not require surgical intervention beyond endoscopy. One patient (patient 7) underwent pleurodesis with cardiothoracic surgery for recurrent pneumothorax and pulmonary blebs but did not require otolaryngologic intervention. The remaining 4 patients (14%) (patients 1-4) with multilevel airway involvement necessitating intervention by pulmonology and otolaryngology services are further discussed herein. The clinical characteristics of these 4 subjects (identical to patients 1 through 4 in Table 1) are detailed in the following case series and summarized in **Table 2**.

### CASE SERIES

This case series describes 4 pediatric patients with WG and multilevel airway involvement whose clinical courses are outlined in Tables 1 and 2. Patient 1 was seen in the mid 1990s, while the others (patients 2-4) were seen in the late 2000s. These subjects were managed by the rheumatology service for laboratory testing and medical treatment both as outpatients and inpatients. Medical treatment for this cohort could be categorized into steroidal anti-

**Table 2. Clinical History of Subjects With Wegener's Granulomatosis and Multilevel Airway Involvement**

Characteristic	Patient No. <sup>a</sup>			
	1	2	3	4
Follow-up since disease diagnosis, y	13	3	7	4
<b>Initial Presenting Airway Lesion</b>				
Subglottic stenosis		X	X	X
Pulmonary nodules	X			X
Bronchial granulation				X
Tracheal stenosis		X		
<b>Airway Lesions Throughout Course of Disease</b>				
Pneumothorax	X		X	
Subglottic stenosis	X	X	X	X
Tracheal stenosis	X	X	X	
Bronchial stenosis			X	X
Pulmonary hemorrhage	X		X	X
<b>Additional Sites of Involvement</b>				
Kidneys	X			X
Nasal		X	X	X
Gastrointestinal tract				X

Abbreviations: X, named characteristic applies to given patient; blank table cell, named characteristic does not apply to given patient.

<sup>a</sup>For more information on the characteristics of these 4 patients, see Table 1.

inflammatory (prednisone), antineoplastic agents (cyclophosphamide, azathioprine, chlorambucil, and methotrexate), immunomodulators (cyclosporine), and monoclonal antibodies (rituximab). All subjects received corticosteroids and antineoplastic agents. The timing of immunomodulator and monoclonal antibody treatment along with the patient's disease course paralleled drug approval by the US Food and Drug Administration and promising scientific publications on treating adults with WG.

### Case 1

Patient 1 initially presented at age 15 years with a rash, arthralgias, and pulmonary hemorrhage. He was diagnosed as having Henoch-Schönlein purpura based on initially negative cytoplasmic ANCA (c-ANCA) findings. Subsequently, he tested c-ANCA positive and had renal and pulmonary pathologic findings consistent with WG. His treatment prior to WG diagnosis was with steroids. He eventually was treated with immunosuppressants and antineoplastic agents and underwent plasmapheresis. Surgically, he required pleurodesis and bleb resection to treat recurrent pneumothoraces. For both subglottic and tracheal stenosis, he underwent endoscopy with dilatation, granulation tissue removal, and steroid injection intermittently over the 9 years following initial presentation. As his hoarseness and stridor continued to progress, he decided to transfer care to Canada, where, at age 26 years, he underwent a cricothyroid resection. At his last follow-up at age 28 years, he continued to have subglottic narrowing and vocal cord paresis resulting from his resection procedure.

### Case 2

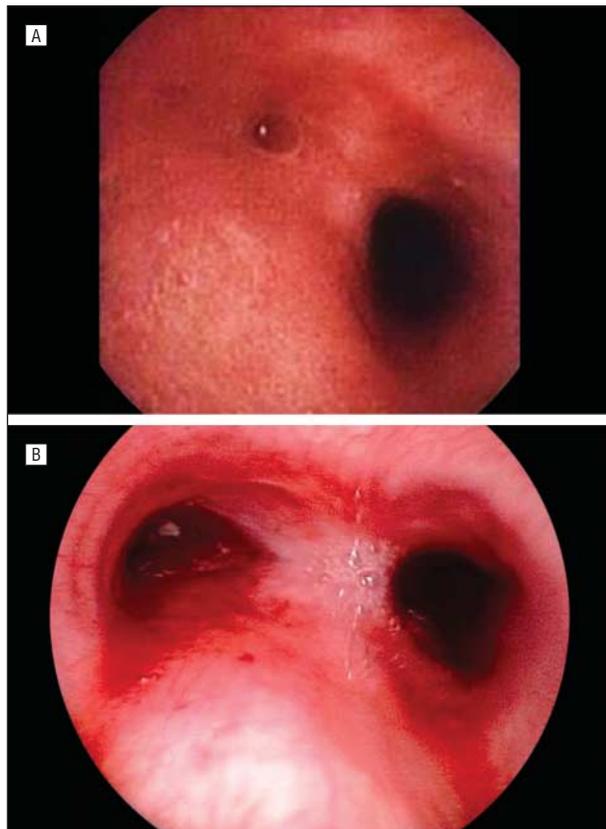
Patient 2 initially presented to the otolaryngology service with a history of eustachian tube dysfunction and chronic sinusitis at age 13 years. The diagnosis of WG was made

based on a positive c-ANCA finding and persistent sinusitis. As her disease progressed, she developed a saddle-nose deformity and subglottic and tracheal stenosis. She was initially treated with steroidal anti-inflammatory and antineoplastic agents. She underwent a total of 5 procedures involving balloon dilatations with carbon dioxide laser excision and/or triamcinolone acetonide injection of subglottic and tracheal constrictions. Two of these procedures were performed at an outside tertiary referral center where she had sought a second opinion. Her symptoms did not significantly improve, and so she began rituximab therapy. She went into remission for 3 months but then began having dyspnea again and required 2 additional dilatation procedures during the year after rituximab therapy. At last follow-up, she had been treated for 3 years without any additional severe exacerbations.

### Case 3

Patient 3 was initially diagnosed at age 8 years as having subglottic stenosis after recurrent episodes of steroid responsive stridor. She also had frequent sinus infections and bouts of otitis media. Initial biopsy specimens of the subglottis did not show vasculitis, and her ANCA findings were negative. However, because of the high likelihood that she had WG, her physicians began treating her with steroids and immunosuppressants. Soon after therapy was started, she tested c-ANCA positive, and her disease progressed to her airway.

Prior to her presentation at our institution, she had undergone numerous sinus surgical procedures and 11 dilatations of her subglottic and tracheal stenosis. On first presentation to our hospital for respiratory distress, she was found to have stenoses in her trachea and left mainstem bronchus. She has since undergone numerous bronchoscopies, angioplastic balloon dilatation, and granulation tissue removal involving both the pulmonology and otolar-



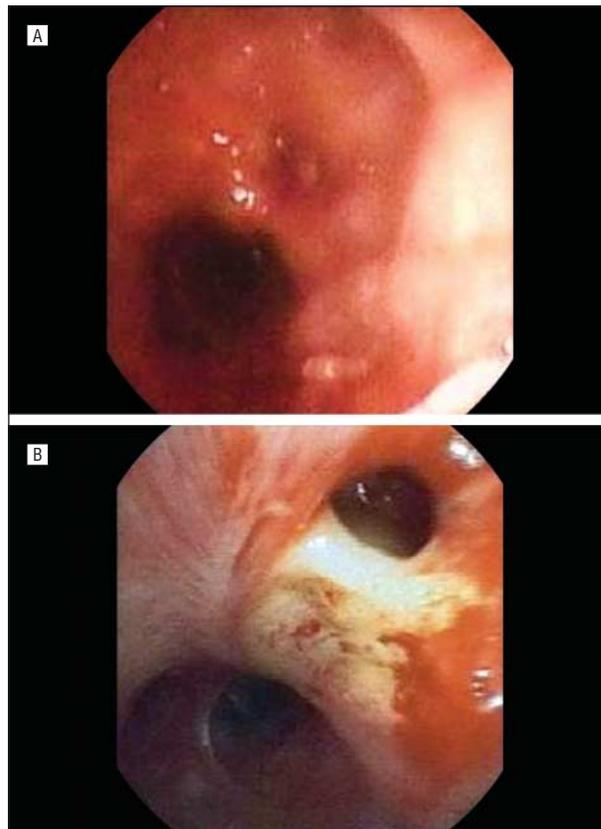
**Figure 1.** Endoscopic photographs of patient 3 showing left main stem stenosis before (A) and after (B) angioplastic balloon dilatation.

ngology services. The utility of angioplastic balloon dilatation in resolving stenoses is illustrated by predilatation and postdilatation endoscopic photographs of this patient in **Figure 1**. Her primary maintenance medical therapy included prednisone, azathioprine, and rituximab.

The patient's treatment course was complicated by a self-limiting pneumothorax that occurred after one of her bronchoscopies with dilatation. Her most troubling ongoing airway complication was the persistent inability to ventilate the superior lobe of her left lung owing to scarring and/or granulomatous overgrowth and recurrent left main stem stenosis. Recently, she underwent a left pneumonectomy by the thoracic surgery service to avert repeated high-risk bronchoscopies with balloon dilatations.

#### Case 4

Patient 4 presented with lymphadenopathy, nephritis, and arthritis at age 14 years. Lymph node and kidney biopsy specimens showed necrotizing granulomatous disease but no vasculitis. Findings for c-ANCA were initially positive. He was treated with steroids for 2½ years and had intermittent gastrointestinal symptoms. He then presented with respiratory distress from subglottic stenosis as well as lower airway granulomas and pulmonary nodules requiring intubation. Treatment with additional steroids, cyclophosphamide, plasmapheresis and rituximab was started. Surgically, we instituted a combined approach with the pulmonary medicine and otolaryngology services to dilate the trachea, right main stem, and dis-



**Figure 2.** Endoscopic photographs of patient 4. A, Significant right main stem narrowing by granulomatous tissue before bronchoscopic removal and angioplastic balloon dilatation. B, Bronchoscopy shows resolution of granulomatous tissue and maintenance of the right main stem patency following rituximab therapy.

tal bronchi and remove granulation tissue. He was extubated after 5 days and continued to improve. His response to treatment, particularly to rituximab, in resolving the right main stem granulation tissue is illustrated in **Figure 2**. His ongoing lower airway issue was the inability to ventilate the superior segment of the right lower lobe owing to scarring and/or granulomatous overgrowth.

#### COMMENT

Pediatric WG is an uncommon disease, and airway involvement either at a single level or at multiple levels was rare in our series (7 of 28; 25%). Presenting symptoms may include constitutional symptoms, renal involvement, and often head and neck disease.<sup>1</sup> Pediatricians are first-line caregivers who evaluate and manage sinusitis, otitis media, and stridor. When standard treatment fails to help these patients, otolaryngology referral should be made, and in turn otolaryngologists must have a high level of suspicion to include WG as part of the differential diagnosis. In our cohort of patients, chronic sinusitis was the most common presenting symptom, and arthralgia, hemoptysis, and nephritis were seen in multiple patients as well. Constitutional symptoms are seen in 96% of patients at presentation, and head and neck manifestations are seen in 84%.<sup>1</sup> Ensuring that such patients with a similar constellation of symptoms are promptly evalu-

ated by the rheumatology service may facilitate earlier diagnosis and treatment of WG.

While ear, nose, and throat manifestations are seen in 91% to 96% of patients with WG throughout the disease course, multilevel airway involvement is not commonly seen.<sup>1,4</sup> Subglottic stenosis is more common in pediatric-onset WG, but it is only present in 4% to 48% of patients with WG overall.<sup>1,4,12</sup> Concurrent pulmonary involvement is present in approximately 17% of pediatric WG patients.<sup>4</sup> In our series, 21% of pediatric patients had subglottic stenosis (6 of 28). Multilevel involvement, including the subglottis and lower airway, was seen in 14% of our cohort (4 of 28).

Multiple approaches have been used to control the airway in WG. Langford et al<sup>14</sup> compiled a review of 43 adult patients treated for subglottic stenosis due to WG. Twenty patients required intervention consisting of intraoperative dilatation with intralesional steroid injection. None of these patients required a tracheostomy. In comparison, 18 patients were not treated using this technique who did require temporary tracheostomy. Similar results were reported by Hoffman et al<sup>10</sup> in 21 adult patients with WG who underwent a mean of 2.4 dilatations. This treatment with or without steroid injection has also been advocated by many other groups for subglottic stenosis related to WG.<sup>7-9,11</sup> The treatment for bronchial obstruction, however, has not been frequently described. Daum et al<sup>12</sup> reported on tracheobronchial involvement in WG that was treated with rigid dilatation, YAG laser treatment, and placement of Silastic (Dow Corning, Midland, Michigan) stents in patients for disease control. Utzig et al<sup>13</sup> described polytetrafluoroethylene stent placement for bronchial stenosis. However, such interventions do not focus on inducing remission or inhibiting the disease process and were exclusively reported in the adult population.

In dealing with a surgical adolescent population, as in our case series, luminal size and length of instrumentation (flexible and rigid scopes) and equipment (angioplastic balloons) creates additional constraints and challenges. At our institution, we refrain from using stents, without knowing the long-term risks of stents and the duration of remission for our patient population. The surgical management of multilevel airway stenoses has evolved into a joint procedure of flexible and rigid bronchoscopy performed by the pulmonology and otolaryngology services, respectively. Flexible bronchoscopy has the obvious advantage of being able to reach into segmental openings. Rigid bronchoscopy, while only able to view a portion of the lung segments, allows more efficient removal of granulation and scar tissue, angioplastic balloon dilatation, and intralesional corticosteroid injections. Although this combined approach has not been completely successful in resolving all lobular (patient 3) and segmental (patient 4) stenoses, it is our hope that manipulation of the medical therapy for these patients may bring about future improvement. The need to perform repeated surveillance endoscopy and the ever-changing endoscopic findings underscore the dynamic nature of this disease in children. We view our current approach to be a workable solution for this complex population.

Rituximab is a new alternative therapy to the traditional mainstay therapies of corticosteroids, immuno-

suppressants, and antineoplastic agents. Prior studies have shown that rituximab can be effective in WG at a dose of 375 mg/m<sup>2</sup> weekly for a 4-week period.<sup>5,6,15,16</sup> Most of these studies have focused on the adult population and often do not include patients with lower airway involvement. Seo et al<sup>6</sup> describe 5 patients with pulmonary nodules and 1 with subglottic stenosis who decreased their steroid dependence or became asymptomatic after rituximab treatment. However, 3 of these patients required a second treatment, and by inclusion into the study all had limited disease (ie, room air saturations, >92% and oxygen pressure, >70 mmHg).<sup>6</sup> In our experience rituximab helped to decrease airway manifestations of WG and prolong periods between surgical interventions. Patient 2 was able to remain asymptomatic for a period of approximately 3 months after starting rituximab treatment. Even after she had a return of mild stridor, her frequency of surgical intervention decreased from 5 times in a year to twice a year. Patient 4 showed a remarkable turnaround after starting aggressive immunosuppression and rituximab therapy. He was weaned from ventilator support, and had only grade 1 subglottic and right lower lobe segmental stenoses with minimal granulation tissue after 3 months of treatment. In our most severe case, patient 3, rituximab in combination with corticosteroids did not alter the frequency of endoscopy and dilatation. Unfortunately, it is difficult to isolate the effects of rituximab from surgical interventions and adjuvant care techniques such as positive pressure assistance or increases in steroid doses.

This study is inherently limited in its retrospective nature and small sample size. The interplay between surgical and medical therapy deemed important by the authors cannot be easily demonstrated owing to the rarity of WG in children and the paucity of multilevel airway disease in those with pediatric WG.

In conclusion, to our knowledge, this study represents the largest reported series of children with WG with multilevel airway involvement. The varied clinical presentation and course of this cohort highlights the need for the otolaryngologist to be keenly aware of this clinical entity because he or she serves as the sentry for the initial diagnosis for most of these subjects. When managing children with WG, and particularly those with multilevel airway disease, it is imperative to involve rheumatology and pulmonology colleagues in a team management paradigm.

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Critical revision of the manuscript for important intellectual content: Eustaquio, Chan, Deterding, and Hollister. Administrative, technical, and material support: Eustaquio, Chan, Deterding, and Hollister. Study supervision: Chan.

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