# The Liverpool Experience: The Role of Immunosuppression in treating Vasculitic Subglottic Stenosis

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September 24, 2021

**Abstract**

Five Key Points * Subglottic stenosis (SGS) is the commonest tracheobronchial manifestation of granulomatosis with polyangiitis (GPA), with early recognition and treatment key to preventing its vasculitic progression and fibrosis. * Previous studies have shown SGS to be the first feature of GPA in 4% of cases. It is not uncommon to see negative biochemical (10% ANCA negative) and negative histological biopsies (77% of head and neck specimens are negative). * Our management strategy emphasized rapid SGS-GPA treatment with limited surgical manipulation of the airway and systemic immunosuppression (IS) to prevent evolution of SGS & concurrent systemic vasculitic relapse. * In our study early multi-disciplinary team involvement to deliver induction IS in the presence of active SGS-GPA led to a procedure free interval (PFI) of 31.3 months. This is a significant increase compared to other published studies. * Nineteen percent (4/21) of the cohort did not require any surgical input following induction IS.

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**MeSH Keywords:** laryngostenosis, acquired subglottic stenosis, Granulomatosis with Polyangiitis, immunosuppressants, Antineutrophil Cytoplasmic Antibodies

*Main Manuscript (Blinded for Review)*

## Introduction

Subglottic stenosis (SGS) is the commonest manifestation of tracheobronchial disease in granulomatosis with polyangiitis (GPA) (8-23% cases).[1] The progression of the inflammatory ring and fibrosis below the true vocal

cords in GPA is dictated by the number of relapses and vasculitic insult sustained. Early recognition and management is imperative in limiting SGS in GPA (SGS-GPA), with otolaryngologists often the first clinician to encounter the disease.[2]

Management of SGS-GPA can be challenging as delayed treatment may cause respiratory compromise, whilst aggressive surgery may trigger a systemic inflammatory response and associated vasculitic complications.[3]There are currently no guidelines for SGS-GPA management. Several different surgical techniques described in the literature,[3] including subglottic dilatation with pulmonary balloons, bougie, rigid bronchoscopy, laser and use of intra-lesional steroid injections. [3,5] However, the impact of systemic immunosuppression (IS) on SGS-GPA management and deferring surgery has not been widely explored.

Our department adopted a combined medical and surgical approach, consisting of subglottic dilatations with systemic steroids given at induction of anaesthesia and systemic IS in the peri-operative period. IS was administered with the view of suppressing any current or potential inflammatory response from surgery.

**Objectives**

We analysed the impact of IS on surgical procedure rates, by comparing our operative rates with other case studies. Patient and disease co-variables' impact on operative rates were also reviewed.

**Method**

**Ethical Considerations**

The study does not represent research, confirmed with the Health Research Authority tool. It was registered as a service evaluation project with the Liverpool University Hospitals NHS Foundation Trust's audit department. The STROBE guideline was used for this manuscript.

**Study Design & Participants**

This was a retrospective single-cohort study, consisting of SGS-GPA patients treated and followed-up between 1st January 2000 to 2nd November 2020. Diagnosis of GPA was considered on the background of clinical, radiological and histological findings.

**Setting: Departmental treatment of SGS-GPA**

Patients were included in this study from the joint ENT and vasculitis multi-disciplinary team (MDT) database. The MDT consists of otolaryngologists with sub-specialty expertise in vasculitis, multi-organ vasculitis consultants and a vasculitis advanced nurse practitioner. Those with suspected or confirmed vasculitis were reviewed for ENT involvement in the joint vasculitis clinic. Patients with significant SGS involvement were consented for airway assessment under general anaesthesia (laryngotracheobronhcoscopy) with/without biopsy and dilatation.

At surgery, high dose intravenous steroid (commonly 500mg - 1g methylprednisolone) was administered at induction of general anaesthesia. The subglottis was dilatated to its normal caliber using either pulmonary balloons (Boston Scientific$^{TM}$) or serial dilatation with bougie.

A multi-organ vasculitis team review was arranged on diagnosis of SGS-GPA.

Patients with a new diagnosis of active SGS-GPA inflammation received induction IS with steroids and Cyclophosphamide or Rituximab. Target date for the start of induction IS was a couple of months prior to surgery where possible, however diagnostic delays and patients with severe symptoms requiring urgent intervention delayed initiation of induction IS in certain instances. Induction IS was administered in accordance with European guidelines concerning Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis.[6]

Symptom review and nasendoscopy was undertaken on follow-up to assess for SGS progression. Patients in remission or exhibiting fibrotic non-active SGS-GPA received maintenance IS, usually consisting of either Azathioprine or Rituximab maintenance therapy.

### Data Sources

Patient demographics, GPA organ involvement, induction IS utilised, investigations, surgical interventions and follow-up data were extracted from the Trust's electronic records system.

The severity of stenosis was classified using the Cotton-Myer (C-M) classification system; an average subglottic diameter taken as 14mm and 17mm for females and males respectively.[4]

Relapses were defined as active inflammatory recurrence in the airway or recurrent SGS requiring further treatment, whilst remission was considered when a patent airway was maintained and no inflammatory recurrence seen.

### Data Analysis

Data was analysed using 'R' software v4.0.5 for Mac IOS. A frailty model (using Cox proportional-hazards regression) was performed to obtain the procedure-free interval (PFI) with IS use. Co-variables reviewed included patient gender, ANCA status, GPA-associated disease progression, type of surgical procedure and C-M grade.

The mean PFI was calculated for comparisons with our cohort & stipulated SGS-GPA studies. This was based on the number of surgical procedures per patient divided by the stipulated average follow-up period.

## Results

### SGS-GPA Cohort & Characteristics

There were twenty-seven patients managed for SGS-GPA in the joint ENT vasculitis clinic between the 1$^{st}$ of January 2000 to 2$^{nd}$ November 2020. Six patients were excluded from our analysis: two were surgically managed outside the region with no management records available and four patients were referred with GPA late into their disease progression, undergoing multiple surgical dilatations with no induction IS.

The average age at diagnosis was 51.1 years (range 21-67), with a female majority (15F:6M). SGS was the initial presentation of GPA in four patients. Other affected sites by GPA in the cohort are summarised in table 1.

### SGS-GPA Investigations

Flexible nasendoscopy & pulmonary function tests were performed in all patients pre-operatively. The average C-M grade on presentation was 1.9 (range 1-3). Computed tomography (CT) or magnetic resonance imaging (MRI) was performed in 18 patients (86%).

ANCA was detected in 12 patients (57%), with the remaining 9 patients treated as ANCA-negative vasculitis. SGS biopsies were taken in 13 patients (62%); the majority showing non-specific inflammation/ fibrosis (11/13), whilst two specimens (2/13) demonstrating GPA through necrosis with focal granulomatosis.

### Management & Follow-up of SGS-GPA

All 21 patients underwent IS on SGS diagnosis; four (19%) required solely medical therapy, with the majority requiring surgical dilatation (81%). Figure 1 displays the individual management pathways of the cohort.

Following dilatation and induction IS all patients remained on maintenance oral IS. Eighteen patients (90%) went into remission, with no further active inflammation reported. Two patients experienced relapse with recurrent SGS during their follow-up period requiring further IS (figure 1 – patients 9 &19).

A total of twenty-nine SGS dilatations (24 bougie & 5 balloon dilatations) were performed. Four of the patients required emergency tracheostomy (patient 9 required a tracheostomy on two separate occasions). All patients were successfully decannulated.

Intralesional steroid (40mg methylprednisolone) was utilised in the four balloon dilatations, with intravenous corticosteroid administered in all procedures. Post-operative complications were experienced following one

balloon dilatation procedure (hospitalisation for pneumonia) and one tracheostomy (pneumothorax). No complications were recorded for bougie dilatations.

The cohort (21 patients) was followed up for a mean period of 59.8 months (range 15.7-201.5 months). One patient died from urosepsis (unrelated to GPA progression).

When calculating the mean PFI; 17 patients underwent 34 procedures were followed up for an average of 66.5 months. The mean PFI was denoted to be a procedure every 31.3 months (range of 5.4- 201.5 months). Figure 2 represents the regression model attained (72% concordance). None of the covariables reviewed showed any statistically significant impact on PFI.

**Discussions**

There are no diagnostic criteria for ANCA-associated vasculitis (AAV).[2] Investigative accuracy has been limited in AAV; 77% of head and neck biopsies are non-diagnostic and 10% of AAV patients being ANCA negative. The latter is accentuated in localised GPA disease such as SGS.[2]

This is echoed in our cohort with 9 ANCA-negative cases and only 23% of biopsies confirming GPA. Considering the low yield of diagnostic tests, we recommend regular clinical assessments for signs of systemic involvement and early MDT input where systemic features of GPA are recognised.

Our medical strategy for SGS-GPA has shown that induction IS for active SGS-disease improves the PFI and decreasing need for more invasive surgery.[7] Comparing with other studies utilizing a surgically centered approach (table 2),[3,8-10] our PFI was notably better, with 19% of the cohort not requiring surgery. This demonstrates a 65% increase when comparing against the mean PFI of the quoted studies at 19.0 months (this was calculated with individual mean PFIs given different weighting based on the study's cohort size).[3,8-10]

Four patients required a tracheostomy for emergency airway management. Ideally all SGS-GPA patients should be managed with an emergency airway dilatation where possible rather than an emergency tracheostomy. However, with the joint ENT vasculitis being a regional service, emergency airway dilatation procedures are not always available in the peripheral hospitals. Nevertheless, the tracheostomy rate in this study (19%) was lower than that quoted in the literature (41-52%),[3] with all patients decannulated promptly.

The benefit of IS is further stated when assessing the four patients excluded from our study due to extensive SGS-GPA and late referral for MDT management: undergoing a combined 54 dilatational procedures, translating to a 6-fold increase in surgeries required in the absence of induction IS. This enforces the message of early MDT management with induction IS.

The regression model estimated an improved mean PFI of 48 months, reflecting a more accurate representation of the mean PFI obtained our patients' individual rates at 42.8 months. Unfortunately, the impact of the other covariables could not be adequately analysed, due to small sample size obtained.

**Conclusions**

A high index of vasculitic suspicion in SGS should be maintained, despite the potential for negative biochemical and histological findings.[2]

Early multidisciplinary input for SGS-GPA with induction IS has reduced the need for surgery: increasing the PFI by 65% when compared to the literature and reducing morbidity otherwise sustained from tracheostomies and other complex surgical interventions.

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*Table & Figure Captions*

**Table 1: GPA Disease Progression in SGS-GPA Patients**

*Abbreviations* ; SGS: Subglottic Stenosis, GPA: Granulomatosis with Polyangiitis

**Table 2: Comparison of Procedure Efficacy**

*Abbreviations* ; SGS: Subglottic Stenosis, GPA: Granulomatosis with Polyangiitis, No.: Number, Trach: Tracheostomies, PFI: Procedure-free Interval, M: Medical Therapy, ILSI: Intra-Lesional Steroid Injection, D: Dilatation, LASER: Light Amplification by the Stimulated Emission of Radiation, LTR: Laryngo-Tracheal Reconstruction/ Resection, MC: Topical Mitomycin C).

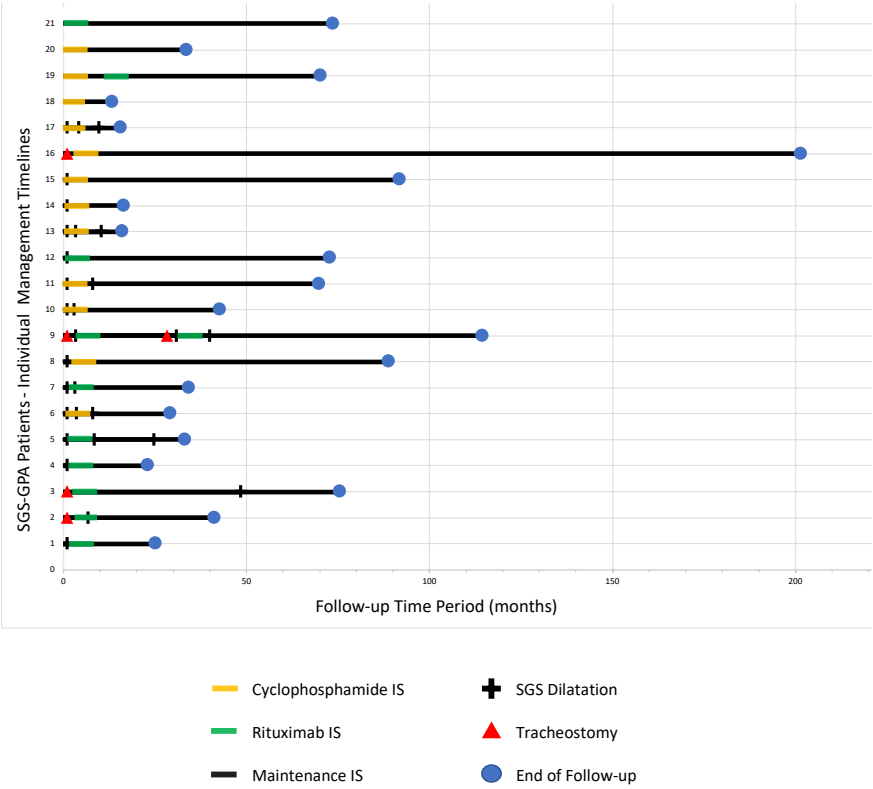
**Figure 1: SGS-GPA Patient Management Timeline**

*Abbreviations* ; SGS: Subglottic Stenosis, GPA: Granulomatosis with Polyangiitis, IS: Immunosuppression

**Figure 2: Frailty Model illustrating Procedure-free interval estimate and its respective confidence intervals**

*Abbreviations* ; SGS: Subglottic Stenosis, GPA: Granulomatosis with Polyangiitis, PFI: Procedure-free Interval

*Marker indicating the mean PFI estimated (48 months)*

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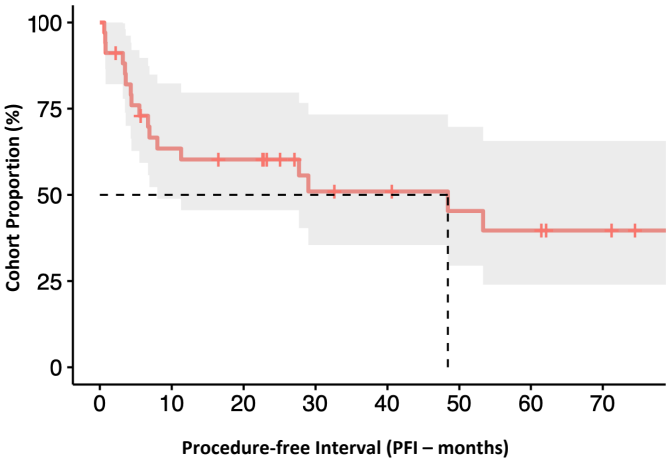


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Abbreviations: No.: Number, Pt: Patient, SGS: Subglottic Stenosis, GPA: Granulomatosis with Polyangiitis

| GPA Site involvement due to Disease Progression | No. of Pts with GPA site involvement (No. of Pts with site involved at SGS-GPA diagnosis) |
|---|---|
| Lung Disease | 10 (7) |
| Sinonasal Disease | 9 (9) |
| Renal Disease | 4(4) |
| Orbital Disease | 4 (4) |
| Cardiac Disease | 4 (1) |
| Otological Disease | 3 (2) |
| Peripheral Nerve Pathology | 3 (2) |
| Musculoskeletal Disease | 3 (0) |

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| ***Author*** | **SGS-GPA Patient No.** | **Mode/s of Treatment** | **Mean Follow-up Period (months)** | **No. of Procedures (No. Trach)** | **PFI** |
|---|---|---|---|---|---|
| *Hoffmann et al. ('03)* | 21 | *0 M*<br>21 S (ILSI+D) | 40.6 | 64<br>(0) | 13.3 |
| *Nouraei et al. ('08)* | 18 | *0 M*<br>18 S (ILSI+D) | 23.2 | 24<br>(0) | 17.4 |
| *Taylor et al. ('13)* | 17 | *0M*<br>17S (D +/- ILSI +/- MC +/- LASER or LTR or T) | 98.0 | *<br>(7) | 18.3 |
| *Gluth et al.* | 27 | *6 M*<br>21 S (D +/- ILCS +/- LASER +/- MMC or LTR or T) | 76.8 | 61<br>(11) | 26.5 |
| *Zammit et al. ('21)* | 21 | *4 M*<br>17 S (D +/- ILSI & LASER or T) | 66.5 | 34<br>(5) | 31.3 |

****Total number of procedures not reported, however PFI was reported as 'days between procedures' in the study***