HHS Public Access

Author manuscript

JAMA Otolaryngol Head Neck Surg. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

JAMA Otolaryngol Head Neck Surg. 2017 June 01; 143(6): 609–613. doi:10.1001/jamaoto.2016.4126.

Inaugural Symposium on Advanced Surgical Techniques in Adult Airway Reconstruction:

Proceedings of the North American Airway Collaborative (NoAAC)

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The North American Airway Collaborative (NoAAC) network is an international voluntary consortium founded in 2014 to advance the science and treatment of adult airway disorders. The collaborative is composed of clinicians and study personnel at more than 50 centers of

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

excellence in adult airway disorders, as well as involved patient partners. The NoAAC aims to continuously improve the quality, safety, effectiveness, and cost of medical interventions in adult airway disorders through support of translation science and the establishment of best practices for diagnosis, evaluation, and treatment.

In support of these goals, NoAAC hosted the inaugural Symposium on Advanced Surgical Techniques in Adult Airway Reconstruction at The Johns Hopkins Hospital in Baltimore, Maryland, on February 22, 2016. The symposium brought together airway experts with diverse skill sets to share ideas and the nuances of their respective approaches to advance the field of adult airway reconstruction. Participants from the United States and the United Kingdom spanned a broad range of disciplines, including plastic surgery, pediatric otolaryngology, laryngology, head and neck surgery, and rheumatology. The result was an interactive educational forum that disseminated diverse practices across disciplines and geography; a landmark event in the intellectual diaspora of adult airway reconstruction. This article presents this experience to the larger scientific community.

Symposium Program

The program consisted of 4 lectures and 5 panels covering basic science, translational research, and advances in surgical techniques. The 4 lectures were titled: microvascular reconstruction of the trachea, human airway remodeling, immunologic and metabolic abnormalities in laryngotracheal stenosis, and molecular diagnosis of orbital inflammatory disease. The 5 panels addressed the following topics: role for free flap reconstruction, novel surgical strategies for idiopathic subglottic stenosis, advanced reconstructive techniques for glottic involvement, techniques learned from the pediatric airway experience, and the role for surgical therapy in autoimmune subglottic stenosis.

Airway Reconstruction Presents a Complex Problem

Adult laryngotracheal stenosis (LTS) is a collection of multiple rare diseases. The etiologies of LTS and approximate percentages include iatrogenic (postintubation) (70%), autoimmune (15%), and idiopathic (15%).[1] Although all etiologies lead to airway obstruction, they occur in unique populations and have different responses to therapy. Improving life for patients with LTS require specific approaches for small, clinically distinct patient populations. Idiopathic subglottic stenosis (iSGS) is mainly a disease of mucosal inflammation associated with activation of the interleukin-17A (IL-17A) pathway. New minimally invasive surgical approaches focus on selective endoscopic removal of affected mucosa, with epithelial reconstitution with antifibrotic dermal grafts (oral presentation and discussion during the symposium unpublished at this time, Reacher and Maddern). The primary autoimmune disease associated with airway compromise is granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis). Diagnosis is clinical, with 20% of GPA patients showing negative results antineutrophil cytoplasmic antibody (ANCA) testing. New biologic therapies are changing the outcome for patients with GPA. Iatrogenic injuries occur in medically vulnerable populations, complicating therapeutic efforts. For small to medium lesions, various portions of the larynx and trachea can be resected and replaced with

adjacent tissue. However, reconstruction of large defects and traditional defects inpatients with comorbid disease presents a considerably more complex set of challenges.

Most applications of complex organ reconstruction involve sterile spaces or ability to transfer vascularized tissue into the diseased area. In contrast, reconstruction of the upper airway, specifically the laryngotracheal complex, is complicated by a constant microbial burden, poor immune defenses and open lumen, proximity to cardiovascular structures, and small-caliber vessels not suitable for microvascular anastomoses. Therefore, unfortunately, the trachea and larynx cannot currently be transplanted reliably. Grillo[2] suggested that the ideal tracheal substitute should be laterally rigid, longitudinally flexible, lined with respiratory epithelium, have initial airtight anastomoses, be able to integrate into adjacent tissue to avoid chronic inflammation, and allow the avoidance of immunosuppressive therapy. Grillo[2] also emphasized that the technique should be straightforward with predictable results. New insights into the science and the clinical art of surgical airway reconstruction of long-segment tracheal stenosis, and tracheal stenosis in complex medical patients were discussed.

Microvascular Reconstruction of the Trachea

Peirong Yu, MD, discussed novel approaches in microvascular reconstruction of the trachea based on his unique experience involving large oncologic defects. He shared his experience in translating animal research to human reconstruction.[3–6] Yu's particular expertise involves single-stage airway reconstruction using free tissue transfer constructs. Yu outlined 4 core principles for airway reconstruction in this setting; (1) recreate the epithelial lining, (2) provide semirigid support to prevent airway collapse, (3) cover the construct externally with well vascularized tissue bulk, and (4) stabilize the construct in the perioperative period with a luminal stent. Similar to Dr Grillo's original criteria, Yu shared that the ideal materials for microvascular airway reconstruction would be noncompressible and flexible, incorporate into surrounding tissues, have a thin internal lining, and use donor tissue with reliable and consistent vascular anatomy.

Yu shared several examples of single-stage large defect airway reconstruction. He noted an approximately 50% decannulation rate following reconstruction in a population where there was no option for primary or local flap repair of the airway.

Immunologic and Metabolic Abnormalities in Laryngotracheal Stenosis

Alexander Hillel, MD, shared his basic science research analyzing the mechanisms behind the robust fibrotic response seen in laryngotracheal injury. His research shows that scar fibroblasts are highly proliferative, have higher collagen 1 expression, and drive proliferation through glycolysis creating a Warburg-like effect, similar to cancer cells that drive rapid growth with a low oxygen demand. The metabolic protein, mechanistic target of rapamycin (mTOR), was chosen for its role in these functions. Rapamycin has several US Food and Drug Administration approved uses and has been shown to reduce fibrosis in experimental models for dermal, cardiac, and hepatic applications; it similarly shows promise for airway stenoses as well.[7] Dr Hillel's research showed that the mTOR inhibitor, rapamycin, has an antifibroblast effect in vitro. Rapamycin shows potential to be a rational and targeted

treatment for laryngotracheal injury and stenosis and warrants further study to develop clinical applications.

Role of Free Flap Tissue Transfer in Airway Reconstruction

Alexander Gelbard, MD, moderated this panel discussion that focused on the role of free flap reconstruction in mecially complex patients. As of the date of the symposium, it is estimated that there are 48 reported cases of microvascular reconstructions of the adult airway. In the setting of stenosis with a protected airway, a multistage approach can be developed. Alexander Langerman, MD, shared his experience with the technique in reconstructing long-segment tracheal stenosis with a mucosa-lined tracheal prefabrication for 8 cm length of stenosis.

Chad Zender, MD, reported on the use of delayed ear cartilage grafting into a supraclavicular island flap for tracheal reconstruction. The supraclavicular artery island flap is a local fasciocutaneous flap harvested from the shoulder and supraclavicular area that has been gaining popularity for reconstruction of head and neck defects. The vascularized composite flap uses the natural curve of conchal cartilage to recreate the curvature of the airway. This technique can be used for segmental tracheal reconstruction and avoids the need for microvascular anastomoses.

Idiopathic Subglottic Stenosis

The pathophysiology of idiopathic subglottic stenosis (iSGS) remains poorly understood, though the patient demographics are quite homogeneous. This progressive fibroinflammatory narrowing of the airway typically affects otherwise healthy middle-aged white women. Currently, knowledge of how to alter the disease process, other than excising the affected structures, is limited. Therefore, several speakers emphasized the considerable value of determining the underlying pathophysiology of this disease. Previously, in the absence of investigation into the basic biology of iSGS, several theories have been embraced regarding the mechanisms involved, including extraesophageal reflux, occult autoimmune disease, hormonal alterations, occult trauma, and bacterial-induced inflammation.[8–14] The association of reflux and laryngotracheal stenosis was not addressed in detail during the symposium, though it has long been debated. Although the mechanism of gastric acid or other refluxate proteins impairing laryngotracheal mucosal wound healing has been shown in animal studies,[15–17] its association with laryngotracheal stenosis in clinic studies has not been as clear. Therefore, discussion during the symposium favored empirical treatment of gastroesophageal reflux in patients with airway stenosis, because there is at least a correlation and the relative benefits in treating airway stenosis likely outweighs risks.[9,14,18]

Human Large Airway Remodeling in Idiopathic Subglottic Stenosis Is Differentially Shaped by the Host-Pathogen Interface

Dr Gelbard described his preliminary investigations into the role of the host-pathogen interface in iSGS. His research used quantitative polymerase chain reaction and immunohistochemistry of iSGS airway scar tissue to demonstrate activation of the interleukin (IL)-17A inflammatory pathway. Flow cytometry identified that the tracheal

IL-17A is derived from Yδ T cells, a unique lymphoid subset responsible for immunity at mucosal surfaces.[19] Although crucial in protecting the host from invasion by many types of pathogens[20] dys-regulated IL-17A production can drive chronic inflammation[21–23] with subsequent tissue damage and fibrinogenesis.[24,25] Human studies in parallel pulmonary diseases strongly support a critical role for IL-17A in the fibrotic remodeling seen in asthma,[21,26] chronic obstructive pulmonary disease,[23] and obliterative bronchiolitis.[24]

Identification of the IL-17 pathway in iSGS is a potential break-through for targeted treatment approaches. Interleukin-17A is known to be involved in the pathogenesis of autoimmune diseases and chronic inflammatory disorders, such as psoriasis, Crohn disease, and rheumatoid arthritis.[27–29] Recently, targeting of either IL-17A or IL-23 have emerged as promising therapeutic strategies in these disorders.[27]

Novel Surgical Strategies for iSGS

Dr Hillel moderated this panel that focused on novel surgical strategies for iSGS. The clinical experience of multiple senior surgeons emphasized the unique nature of iSGS, with isolated fibrosis limited to the mucosal lamina propria of the mucosa without affecting perichondrium or cartilage. Newer therapies are aimed at selectively removing the affected mucosa while leaving the underlying cartilaginous superstructure intact.

Jan Kasperbauer, MD, shared the Mayo Clinic technique in treating iSGS performing carbon dioxide laser wedge excisions, steroid injection, and mitomycin-C application. This technique is designed to mimic the approach to skin keloids typically employing careful excision and steroid injection. He performs wedge resections dependent on the character of the scar. Violation of the perichondrium is avoided and no balloon dilation is performed. The protocol also calls for an aggressive medical regimen for 1 year after the procedure, including trimethoprim/sulfamethoxazole (or clarithromycin substituted in the setting of medication allergy), maximum-dose proton pump inhibitor, and inhaled corticosteroids. When all 3 medications are used together, this approach was associated with reduced rates of recurrence.[30]

Guri Sandhu, MD, discussed the development of a novel procedure to resect subglottic stenosis that he has termed the “Maddern procedure.” Although endoscopic procedures to treat iSGS often result in predictable recurrence, voice quality remains stable.[31] In contrast, cricotracheal resection has been shown to be curative, but can considerably alter the voice quality in female patients.[32,33] Therefore, because the cartilage framework is not the problem with this disease, he sought an approach to combine the benefits of both techniques. This procedure involves resection of the mucosa with optimized wound healing to reduce scar formation using a temporary split thickness skin graft.[34,35] With this approach, the diseased mucosa is removed while avoiding alteration of the cartilage framework.

The concept of this approach borrows from the hand surgery techniques used for Dupuytren’s contracture. Isolated fasciectomy is associated with high recurrent rates, but dermofasciectomy with skin grafting shows reduced recurrence rates and less fibroblast activity in the skin grafted areas.[36] Finally, more recently mitomycin-C has been avoided owing to lack of established benefit and occasional inflammatory reaction.

Robert Lorenz, MD, described a similar technique termed the retrograde endoscopically assisted cricoid hypertrophic epithelial resection (REACHER) procedure aimed at removing the diseased mucosa and leaving the cartilage framework intact. This procedure is performed through a neck incision; an opening in the airway is made 1 ring below the cricoid to allow access into the cricoid lumen. Endoscopes are then used to assist in complete resection of the involved mucosa and lamina propria using a cold technique. A silicone stent approximately 1.5 cm in length is wrapped in a thin nonadherent dressing and then a split-thickness skin graft. Again, it was noted that exposed silicone leads to granulation and eventual scar formation. Therefore, excess skin graft is used to prevent unexpected exposure of the silicone during healing. The same postoperative considerations for treatment of airway keratosis are required. This technique uses a minimally invasive open approach to excision of the mucosa and modulating the wound healing response with a skin graft.

Posterior Glottic Stenosis

Advanced Reconstructive Techniques for Glottic Involvement

Paul Bryson, MD, moderated this session on advanced reconstructive techniques for glottis involvement. Laryngeal obstruction presents a particularly difficult challenge owing to the 3-way tug of war that exists between the functions of airway, voice, and deglutition in the larynx. In contrast to the problem of maintaining a lumen for respiration in the more distal airway, the larynx requires a delicate balance of form and function. Laryngeal narrowing typically comes in the form of bilateral vocal fold immobility owing to cricoarytenoid joint fixation or recurrent laryngeal nerve paralysis or posterior glottic stenosis with tethering of the vocal folds. Typically the best of all functional outcomes is achieved with a tracheostomy tube to bypass the airway and speaking valve to support the voice. However, the impaired quality of life with a permanent tracheostomy can be unacceptable for the patient. Therefore, techniques to address this problem without continued use of a tracheostomy attempt to strike an acceptable compromise on function with selective augmentation of the airway.

Christopher Wootten, MD, described his approach of endoscopic posterior cricoid split with rib cartilage grafting to augment the posterior airway.[37] Dr Sandhu discussed his approach to augment the posterior airway for laryngeal obstruction by laryngofissure. One of the complications of this approach is to damage the vocal fold by entering the larynx off of midline. He described use of a right angle probe to retract the larynx open from inferior and using a sharp instrument inside to out to avoid cutting the vocal fold itself. This technique also uses rib cartilage as a graft in an inverted T strut. The graft is designed for distraction of a desired width, but 4 mm to 7 mm is usually adequate. Drs Wootten and Sandhu both use split-thickness skin graft–lined stents during the healing phase of the graft as described above for subglotticstenosis. These reconstructions require a tracheotomy during stenting phase of reconstruction.

Techniques Learned From the Pediatric Airway Experience

James Daniero, MD, moderated this session, which examined how the pediatric airway experience can help inform the development to new multidisciplinary treatment algorithms.

The pediatric otolaryngology airway experience, through pioneers such as Robin Cotton, MD, has developedthetypeofalgorithmicapproachtolaryngotrachealrecon-struction that is lacking in adult airway treatment. This is owing to a cohesive group of surgeons collecting data and sharing experiences. In contrast, the community treating adult airway disease is fragmented, with specialists from thoracic surgery, interventional pulmonology, otolaryngology–head and neck surgery, laryngology, and general surgery. The underlying biology of disease in adults and children may be unique, and children seem to have more reliable outcomes, likely owing to their predictable tissue response. Despite the differences, there is much to learn in the exchange of ideas among adult and pediatric airway surgeons. The mission of NoAAC is to bring these groups together for this purpose. To this aim the experts in pediatric airway reconstruction shared their experiences using endoluminal stenting, expansion grafting with anterior and posterior costochondral cartilage grafts, and the use of the slide tracheoplasty. Critically, the pediatric experience has also integrated multispecialty evaluation, including gastroesophageal reflux disease, dysphagia, inflammatory biomarkers, and biofouling and/or methicillin resistant *Staphylococcus aureus* (MRSA) carriage tightly into the preoperative workup for open surgical airway reconstruction.

Alessandro de Alarcon, MD, provided insights on stent placement and subsequent treatment and demonstrated the creative use of balloon dilation through a stent kinked within the airway with a narrow lumen, rather than complete removal, balloon dilation, and repeat replacement.

Dr Wootten discussed the use of anterior and posterior cartilage grafting in adults. He has used the technique in a series of 16 adults with ages ranging from 60 to 80 years with a decannulation rate above 80%. Wootten also noted that in adults, partial graft resorption is acceptable and may act as a spacer that fills in with fibrotic tissue maintaining an adequate level of distraction and airway patency for a durable effect.

Michael Rutter, MD, shared that historically there have been only 2 pathways of intervention for severe laryngotracheal stenosis, graft airway augmentation or excision, often in the form of cricotracheal resection. However, slide tracheoplasty was introduced by Tsang[38] in 1989 and then popularized in children by Rutter beginning in 2001.[39] Slide tracheoplasty is now the treatment of choice for complete tracheal rings and often a first-line treatment for tracheal stenosis because it not only just restores the trachea, but it oversizes it. The tracheal circumference is doubled, which therefore doubles diameter and theoretically increases airflow 16 times (Poiseuille’s law). He demonstrated his technique used in 140 cases and explored applications for tracheal stenosis that could be applied to adults.

During the panel discussion, it was noted that the airway team at Cincinnati Children’s Hospital cultures indwelling tracheostomies preoperatively and screens for MRSA by nasal swab to reduce perioperative infection and loss of cartilage grafts. Furthermore, they use perioperative intravenous vancomycin for several doses in many cases.

Autoimmune Disease in the Adult Airway

Molecular Diagnosis of Orbital Inflammatory Disease: Implications for Idiopathic Subglottic Stenosis

Cailin Sibley, MD, reported on the molecular diagnosis of orbital inflammatory disease using molecular profiling of gene expression signatures. This approach helps to better define autoimmune diseases, rather than other approaches based on variable phenotypes and limited biopsy material. In the setting of GPA, often there are insufficient clinical or histopathological features to establish the diagnosis. Gene expression was quantified from hybridized RNA using GeneChip microarrays (Affymetrix).

This gene expression algorithm was able to differentiate these diagnoses to a greater degree of specificity than standard methods, suggesting the information available in gene expression profiling adds to the diagnostic process independent from the visual clues evident on histopathological examination.[40] Many patients with GPA have a limited form of the disease involving tissues such as sinus, sclera, orbit, nasal mucosa, or subglottis and ANCA results are often negative in limited disease.[41] Furthermore, a definitive diagnosis from biopsy of these tissues is unlikely because the medium-sized vessels that are required to make the diagnosis are not typically obtained in the specimen. This is especially important with regions such as the eye and subglottis, where it is difficult to obtain a large tissue biopsy sample.

Currently the project is focusing on nonspecific inflammatory conditions of subglottic stenosis. Extending this approach to GPA-associated subglottic stenosis and idiopathic subglottic stenosis has implications for early identification and intervention that could fundamentally change the way we think of these diseases. Granulomatosis with polyangiitis-associated subglottic stenosis is primarily a medical disease that occasionally requires salvage surgical intervention in the airway. Therefore, proper identification of the patients leads to earlier medical control that would likely translate into less need for emergent airway intervention.

Role for Surgical Therapy in Autoimmune Subglottic Stenosis

Simon Best, MD, moderated this panel that discussed the role of surgery in autoimmune subglottic stenosis.

Surgical treatment of autoimmune-associated subglottic stenosis becomes complicated in that the medical control of the underlying disease has more influence over the outcomes than the procedure itself. Dale Ekbom, MD, stressed that medical management was the first-line treatment, unless there is a critical airway stenosis. Therefore, collaboration is key with either a pulmonologist or rheumatologist. There has been considerable research in ANCA-associated vasculitis (AAV), of which GPA is 1 of the 3 vasculitides; microscopic polyangiitis and eosinophillic GPA are the others. Typically, initial medical management begins with methotrexate and steroids. Recently rituximab has been extraordinarily helpful for moderate to severe AAV. The RAVE (Rituximab in ANCA-associated Vasculitis) trial was important to show that rituximab is effective compared with cyclophosphamide, which can cause infertility and later hematologic malignant abnormalities.[42]

Ahmed Soliman, MD, presented case examples of GPA-associated SGS requiring surgical intervention. He noted that the surgery is similar to that of other subglottic stenoses and carbon dioxide laser is not seen as a contraindication. However, recurrences are common and perioperative medications are key.

Joshua Schindler, MD, presented complicated GPA airway cases. He noted that airway crusting often complicates the situation. This can produce an acutely obstructive event, even when associated with a noncritical stenosis and necessitates removal in the operating room urgently.

Conclusions

The inaugural symposium of NoACC provided an excellent opportunity for the participants to share their groundbreaking research and considerable clinical insights. It is throuh collaborative efforts, such as those achieved during the symposium, that improvements in the science and clinical treatment of adult airway stenosis will be achieved. Exciting new data and refined techniques presented during the symposium show promise for unlocking improved and patient-specific treatment algorithms.

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