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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

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Swallowing and laryngeal complications in lung and heart transplantation: Etiologies and diagnosis

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KEYWORDS:
swallowing;
laryngeal;
voice;
dysphagia;
dysphonia

Despite continued surgical advancements in the field of cardiothoracic transplantation, post-operative complications remain a burden for the patient and the multidisciplinary team. Lesser-known complications including swallowing disorders (dysphagia), and voice disorders (dysphonia), are now being reported. Such disorders are known to be associated with increased morbidity and mortality in other medical populations, however their etiology amongst the heart and lung transplant populations has received little attention in the literature. This paper explores the potential mechanisms of oropharyngeal dysphagia and dysphonia following transplantation and discusses optimal modalities of diagnostic evaluation and management. A greater understanding of the implications of swallowing and laryngeal dysfunction in the heart and lung transplant populations is important to expedite early diagnosis and management in order to optimize patient outcomes, minimize allograft injury and improve quality of life.

J Heart Lung Transplant 2021;40:1483−1494

Heart and/or lung transplantation is the preferred treatment for end stage cardiac and/or pulmonary disease with the provision of increased survival and quality of life. Recent advances in surgical technique and immunosuppressive medications have increased life expectancy, however complications post transplantation such as primary graft dysfunction, rejection, multi-organ failure and infection remain common.[1-7] There is now growing interest in the lesser known complication of laryngopharyngeal dysfunction (LD), presenting as swallowing disorders (oropharyngeal dysphagia OPD) and voice disorders (dysphonia).[8-13] Current literature reports a high incidence of these complications with findings of OPD in 70% of patients following

Abbreviations: FEES, flexible endoscopic evaluation of swallowing; ICUAW, intensive care unit acquired weakness; LD, laryngopharyngeal dysfunction; LPR, laryngopharyngeal reflux; OPD, oropharyngeal dysphagia; PED, post extubation dysphagia; PPI, proton pump inhibitor; RLN, recurrent laryngeal nerve; SLP, speech language pathologist/pathology; VAD, ventricular assist device; VFP, vocal fold palsy/paresis; VFSS, videofluoroscopic swallow study.

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1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2021.08.006

lung transplantation[12] and a high proportion of vocal fold palsy (paralysis or paresis) (VFP) with incidence ranging from 2.9 % to 34%.[9,14] OPD is well recognized as a risk factor for increased morbidity and mortality[15,16] and is estimated to cost more than US $500 million per year.[17] LD following surgery is frequently associated with incompetence in airway protection with associated risk of aspiration, poor secretion clearance and increased morbidity and mortality.[18-20] Resulting changes to voice quality are known to impact heavily on quality of life and occupation.[21,22]

The potential etiology of voice and swallowing complications in this patient population is poorly understood and has received little attention in the literature. Cardiothoracic transplant surgery and the post-operative course are inherently complex and can involve (1) compromised respiratory function, (2) prolonged intubation,[23-26] (3) damage to the recurrent laryngeal nerve (RLN),[10,14,27] (4) intensive care unit acquired weakness,[28] (5) alterations to neurological status[9,28] and (6) chronic gastro-oesophageal reflux.[29-31] All these factors are known to have a direct association with swallowing and voice dysfunction. The immunosuppression requirements following transplantation also leave patients at higher risk for deterioration in respiratory function in the event of glottic incompetence and/or dysphagia. Patients awaiting transplantation are often frail with poor physiological reserve, rendering them more vulnerable and at higher risk of increased hospital length of stay and adverse post-operative outcomes.[32,33] The prevalence and impact of pre-transplantation OPD and dysphonia are unknown in this complex population.

The aims of this review paper are to (1) provide a comprehensive discussion of the potential etiology for OPD and dysphonia in heart and/or lung transplantation, (2) explore the methods for diagnosis of these complications and, (3) discuss management strategies to help to reduce the burden of disease for this high-risk patient population.

Normal swallowing and vocal function

Normal swallowing is a highly complex neuromuscular process modulated by the central nervous system. Co-ordination of respiration and swallowing is required via the exhale-swallow-exhale pattern to reduce the risk of aspiration.[34-36] Airway protection is a multi-step process, involving movement of the arytenoids to contact the epiglottis, the epiglottis covering the arytenoids and closure of the vocal folds to seal the glottis.[37] Timely adduction of the vocal folds, which is followed by a brief period of apnoea, requires functioning of both superior and RLN's,[38] both of which can be impacted by lung and heart transplant surgery. If vocal fold closure is mis-timed or incomplete, there is a risk of food and fluid entry into the airway. Should this occur, the final airway protective mechanism is a cough reflex which requires not only the motor initiation of abdominal, intercostal and diaphragm muscles and glottic closure but also an intact sensory system to detect the need for a motor response.[38]

Normal voice production is also an intricate process, requiring precise interaction of a number of bodily systems.[39] The RLN supplies all intrinsic muscles of the larynx while the superior laryngeal nerve innervates the cricothyroid muscle to tense and adduct the cords.[40,41] The vocal folds must be able to adduct to the midline and sufficient subglottic air pressure must be produced to enable vocal fold vibration and subsequent phonation. Clear voice production can be compromised by structural or functional asymmetry of the true vocal folds and/or recruitment of supraglottic structures, as well as inflammation or scarring of the vibratory layer of the folds.[40,41]

Etiology of swallowing and voice disorders

Given the highly complex integration of sensory and motor function required for swallowing and phonation, disruption to any element of these pathways can result in dysphagia and/or dysphonia. Dysphagia can present as oropharyngeal dysfunction and/or oesophageal dysmotility following heart or lung transplantation and may be identified following extubation in the intensive care unit with pain on swallowing, dyspepsia, chronic cough, difficulty in swallowing secretions, or coughing on intake of food or fluids.[9,42] Dysphonia may present as hoarse or absent voice or weak cough and may indicate glottic incompetence, risk of aspiration with associated chest infection and potential for respiratory distress.[10]

The potential mechanisms for dysfunction in swallowing and voice following transplantation in this population are discussed below (see also Figure 1).

Respiratory function

The association between respiratory function and swallowing is well established. Following heart and/or lung transplantation, respiratory status frequently remains compromised, at least in the early stages post extubation. Currently there is no literature addressing how the altered respiratory pattern of patients following heart or lung transplantation may affect swallowing function. However, alterations to respiratory physiology, characterized by hypercapnia, tachypnoea or hypoxemia are known to cause a discoordination of the breath swallow cycle and hence an increased risk of laryngeal penetration and/or aspiration, especially amongst the critically ill.[43-45]

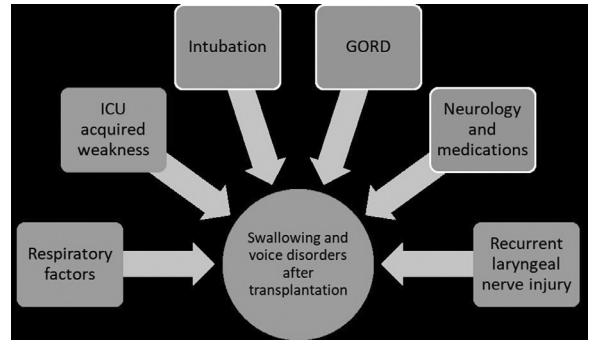


Figure 1 Potential mechanisms for OPD and dysphonia in heart and/or lung transplantation.

The placement of high flow nasal cannula after weaning from the ventilator is a positive step to enable oral intake, however the literature is contradictory as to whether such support assists swallowing safety or increases the risk of aspiration.[46-48]

Optimal functioning of the entire respiratory system is also vital for successful voice production. The subglottic vocal tract is responsible for generating the essential airflow which travels between the vocal folds to act as the power source for the voice.[41,49] Any surgery that impacts on the structure or function of the principal muscles of inspiration or expiration can have an impact on the power source for the voice.[41] Although there is a distinct lack of evidence in this field in regard to the association between respiratory compromise and voice production, diseases which affect expiratory airflow, such as asthma or chronic obstructive pulmonary diseases have been shown to have a negative effect on the voice.[40,50,51]

Intubation

The requirement for endotracheal intubation to allow for mechanical ventilation during heart and/or lung transplantation is another mechanism for the development of laryngeal dysfunction and OPD. Laryngeal injury with associated dysphonia, as a result of intubation, is reported to be as high as 83% in patients within the intensive care unit who require mechanical ventilation.[45] Prolonged intubation is a known independent predictor of dysphagia.[38,52,53,54-56]

Laryngeal damage

Laryngotracheal injuries in this population are common, with the present authors previously reporting dysphonia in 63% of patients referred to speech pathology following transplantation.[42] Intubation related injuries include granulomas, stenosis, infections, glottic and subglottic oedema and vocal fold motion abnormalities due to arytenoid dislocation or nerve damage.[45,57-60] Injury can occur at the time of tube placement, due to prolonged presence of the tube in the airway or at a later stage due to abnormal healing of the airway mucosa. Location and severity of injury can also be associated with the type of endotracheal tube and cuff volume, pressure and location.[61]

'Prolonged intubation is generally associated with mucosal damage such as ulceration and oedema, however peripheral damage of the RLN can also occur due to longer term compression.[62] Extended duration of intubation has been reported to be linked to more frequent and more severe injuries,[45,63,64] however other authors have found no such association.[58]

Post extubation dysphagia

Post extubation dysphagia (PED) is multifactorial and common. Incidence is reported to vary from 3% to more than 80%[52,55,65-67] with a general consensus that the presence of PED results in an increase in hospital length of stay, hospital costs and mortality.[52,68,69]

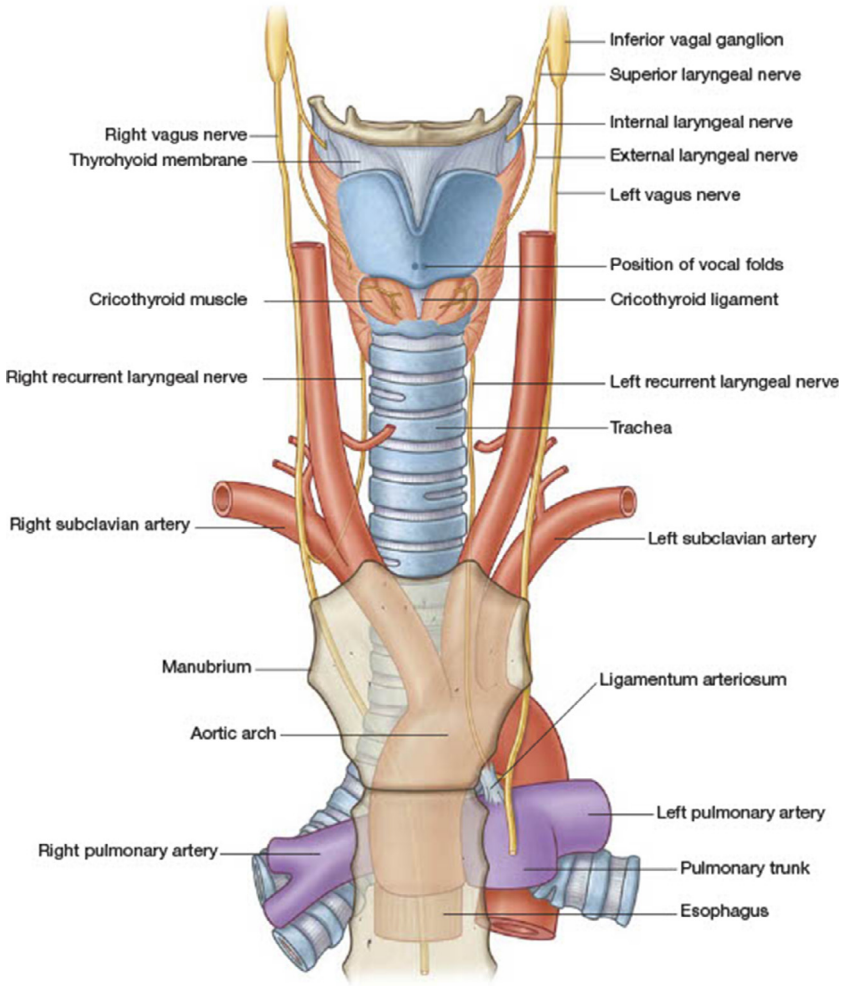
Due to the pivotal role of the larynx in the protection of the airway, the presence of laryngeal pathology post extubation can directly impact on swallowing function.[45] VFP can result in glottic incompetence with an associated high risk of aspiration.[58,70] In addition, laryngopharyngeal sensation can be impacted by the constant pressure of the tube on the chemoreceptors and mechanoreceptors in the pharynx and larynx which have a direct role in the initiation of the swallow.[71] Silent aspiration, defined as the entry of a food or liquid bolus below the level of the vocal folds with no cough reflex elicited, has been reported to be common in the lung transplant population.[8,12] The exact cause for this is unknown, however intubation trauma, laryngopharyngeal reflux, as well as the possibility of direct vagal nerve injury and RLN injury, are all potential contributors.

The most widely reported risk factor for PED is increased duration of intubation.[52,54,66,72,73] However, the literature is conflicting with some authors reporting no association.[74-76] Within the heart and lung transplant populations, the current authors have previously reported duration of intubation and number of intubations to be significant predictors for referral to speech pathology for the management of OPD and voice complications.[42]

Recurrent laryngeal nerve injury

Due to the complexity of heart and/or lung transplantation surgery and the post-operative pathway, it is difficult to determine whether RLN injury or intubation trauma is the primary mechanism for VFP and/or dysphonia. However, the close proximity of the RLN and vagus nerves, which supply all intrinsic muscles of the larynx, sensation for the upper oesophagus and contractility of the digestive tract, to the cardiovascular structures involved in heart and lung transplantation, result in risk of intra-operative injury[77] (see Graphic 1).

Laryngeal complications, especially VFP, are well recognized in the cardiothoracic literature,[77-82] and unsurprisingly, the presence of VFP is reported to have a significant association with OPD in this population.[9,12] Surgery specifically involving the aortic arch is associated with a higher incidence of RLN damage due to the greater risk of direct manipulation.[18] Numerous intra-operative mechanisms for RLN injury in cardiac surgery have been reported, including hypothermia, cardiac catheterization and sternal retraction following sternotomy. In addition, extracorporeal membrane oxygenation has been reported to pose a risk, due to the need for manipulation of the common carotid artery and internal jugular vein which can result in injury to the vagus nerve.[77] However, the specific pathophysiology of RLN injury during cardiothoracic transplantation has been poorly explored. Murty et al[27] report the nerve to be at greatest risk when removing the recipients organs and that the left recurrent laryngeal branch is at higher risk due to its longer course into the posterior mediastinum. This would appear to be supported by increased rates of left sided VFP.[10,14] In addition, Taeneka and colleagues report ventricular assist device implantation to be a high risk for severe VFP which they hypothesize to be potentially related to nerve compression from enlarged cardiovascular structures or direct manipulation and retraction of the heart.[20] Given an increasing proportion of patients with end stage



Graphic 1 Recurrent laryngeal nerve pathway.

cardiac failure are now being supported via ventricular assist device's, the implant/explant of these devices is likely to further the risk of RLN damage.

There is a scarcity of literature addressing techniques to minimize RLN injury during transplantation, however Huddleston and colleagues suggest leaving a small island of pulmonary artery at the insertion of the ligamentum arteriosum, (which joins the pulmonary artery to the aorta), during cardiopneumonectomy in order to lessen the risk.[83]

Incidence of laryngotracheal complications following heart transplantation is reported to be up to 34%[63] with rates of VFP of 2.9%.[14] Higher rates of VFP are evident amongst the lung transplant population with incidence ranging from 8-34%.[9,10,12] Interestingly, Seeliger and colleagues[10] reported that half of their cohort diagnosed with VFP were asymptomatic. This phenomena has also been reported in other surgical procedures which place the RLN at risk.[84,85] Hence, it could be argued that pre-operative laryngoscopy should be conducted in patients awaiting transplantation who have a history of thyroid, skull base, carotid, anterior approach to cervical spine, or esophagectomy surgery. In addition, formal screening of vocal fold function for all patients following lung transplantation is recommended.[10]

ICU acquired muscle weakness (ICUAW)

Patients who experience complications during and following heart and/or lung transplantation are frequently in an induced coma for long periods of time with high levels of sedating medications, high dose corticosteroids, potential sepsis and/or multi organ failure and hence are at high risk of ICU acquired weakness (ICUAW).[28,86] ICUAW can manifest as neuromuscular disorders of critical illness polyneuropathy or myopathy which is associated with prolonged weaning from ventilator support and increased length of stay.[87,88] Despite the scant data, incidence among lung transplant patients is reported to be as high as 29% with a median post-transplant latency of 35 days.[28]

Muscle atrophy, as a component of ICUAW, is known to have a profound effect not only on peripheral muscle strength but also inspiratory and expiratory muscles which are required[89] for voice production and cough effectiveness. Impairment of these functions are known to be a strong predictor for both reintubation[89-91] and aspiration.[92,93]

The high frequency of dysphagia in patients requiring ICU admission is well reported[56,65,94] but there is little information on the specific association between ICUAW

and swallowing dysfunction and no data in the area of vocal function. High aspiration rates of liquids and saliva are reported, 78% and 48% respectively.[95] Ponfick and colleagues reported that dysphagia completely resolved in 95% of their cohort within 4 weeks however other studies report 1 to 2 months was required before the ability to swallow fluids was regained.[95,96]

The ability to predict pharyngeal dysfunction and risk of aspiration based on muscle strength before and after transplantation could be a useful tool for early intervention in this high risk population. Mirzakhani and colleagues[97] found that 70% of patients with muscle weakness (defined by the MRC muscle scale score[98,99]) showed symptomatic aspiration events and muscle weakness was associated was an almost ten-fold increase in aspiration risk.

Gastric motility disorders

Disorders of gastric motility, including gastroesophageal reflux disease (GERD), esophageal dysmotility and gastroparesis are common in patients with advanced lung disease, including those with idiopathic pulmonary fibrosis and connective tissue disorders.[100-103] Several studies report the prevalence of gastric motility disorders to increase following lung transplantation[101-103] with the incidence of GERD reported to be as high as 75%.[29-31] The etiology is often multifactorial, however vagal nerve injury, which may occur during dissection for pneumonectomy or during implantation of the donor lungs, as well as immunosuppressive medication regimes, are considered to be large contributors.[104,105] GERD is a known risk factor for the development of BOS (Bronchiolitis Obliterans Syndrome), the pathologic process of chronic rejection following lung transplantation, and hence increased morbidity and mortality.[106,107] As a result, some studies advocate for early diagnosis and aggressive management via both medical and surgical means.[106]

The strong association between GERD and aspiration has been extensively reported[108,109] and its presence prior to lung transplantation has been reported to independently predict OPD.[11] GERD leads to an increase in quantity of gastroduodenal contents within the esophagus and esophageal dysmotility, combine with gastroparesis, can lead to delayed clearance of this material. When these factors, combine with supine positioning, high levels of sedating medications, tube-based- enteral feeding, and immunosuppression medications, there is a predisposition to aspiration events.[110] Furthermore, those undergoing heart and/or lung transplantation are at higher risk of vagal nerve injury which is known to impact on esophageal motility and cause delayed gastric emptying[105,109]

Laryngopharyngeal reflux (LPR), defined as the retrograde flow of gastric contents into the larynx, oropharynx and/or nasopharynx is a common and potentially debilitating component of GERD.[111] Presenting features can include oedema of the larynx on laryngoscopy, throat irritation and/or globus pharyngeus. LPR is known to have a direct impact on laryngopharyngeal sensation and hence airway protection during swallowing[112] and is strongly associated with voice changes. Dysphonia is often cited as the most common extra-esophageal symptom being reported in up to 71% of patients with LPR.[113]

Diagnosis of GERD is frequently made based on the presence of symptoms which may be laryngeal and/or pulmonary in nature, however patients with GERD can also be asymptomatic in this population. Given the significant potential impact of GERD on the presence of BOS and associated graft survival, early and more systematic evaluation, including high resolution esophageal manometry, is generally recommended.[114,115]

The literature supports aggressive management of GERD via both medical and surgical means.[106] Medical management of gastric motility disorders generally involves a combination of lifestyle modifications, (such as diet changes and postural manipulations when eating and sleeping), combined with pharmacological agents such as anti-emetics and prokinetics for gastroparesis[116] and proton pump inhibitors (PPI) for GERD which stop acid production.[104] However, because PPI medications do not stop the process of gastroesophageal refux, non -acid refluxate can still be aspirated with an associated concern for injury to the transplanted organs.[104] For patients that exhibit ongoing GERD symptoms, despite maximal medical therapy, laporoscopic fundoplication may be considered appropriate to reduce chronic damage to the graft and improve survival.[101,117]

Neurology and medications

Other mechanisms for the development of OPD and/or dysphonia following transplantation include transient alterations to neurological function in the context of sedating medications and ICU related delirium, or more serious longer term insults such as intra or post-operative stroke. There is limited data regarding the impact of altered sensorium on swallowing function; however a greater aspiration risk has been reported for those not oriented to person, place and time.[118]

The impact of medication regimes on pharyngo-oesophageal function following transplantation must also be considered. Immunosuppressant drugs used to prevent allograft rejection, including mycophenolate, steroids, and calcineurin inhibitors are known stomach irritants which also cause gastroparesis.[106,119] As a result, it is commonplace to prescribe a PPI and prokinetics to reduce the risk of oesophagitis and micro aspiration of reflux materials as explained above.[9,106] Medications that impact on the central nervous system are reported to be frequently prescribed,[9] with an associated risk of decreased awareness and reduced voluntary muscle control.[120] Furthermore, medications that cause xerostomia or have a known side effect of oesophageal dysmotility are common. Although these medications may be an essential component of the transplantation journey, the multidisciplinary team need to work together closely to understand the interaction and impact of medications on swallowing function.

Risk factors

Definitive risk factors for the development of OPD and dysphonia following heart and/or lung transplantation are

poorly understood (Table 1). As a result of the scant and conflicting nature of the data surrounding pre and post-operative risk factors, robust prospective studies are needed in this field in order to form any conclusions to guide clinical practice.

Evaluation and diagnosis

Within Australian transplantation units, assessment of swallowing and voice function is not conducted as a routine element of the transplantation workup process, but rather referral is made to a speech language pathologist (SLP) if any concerns are raised by the patient or the multidisciplinary team. Following transplantation, OPD and dysphonia, may present after extubation and should trigger referral to SLP for formal assessment.

Dysphonia

Screening for dysphonia at the bedside is usually conducted by a SLP following concerns regarding perceptually abnormal voice. Subjective voice tasks can include maximum phonation time, s/z ratios, pitch range, auditory-perceptual evaluation of voice quality in conversational speech, and sustained phonation. These tasks can be easily conducted at the bedside in the ICU, depending on patient cognition and medical status, and can be indicators for potential referral for further investigation by a laryngologist. The s/z ratio has been shown to have significant accuracy for detection of laryngeal pathology amongst dysphonic patients in other clinical populations[121] and is reported to have a high positive predictive value for the diagnosis of impaired vocal fold mobility post intubation.[122] However, the predictive accuracy for detection of laryngeal pathology via such subjective measures is currently unknown amongst a cardiothoracic transplant population.

Laryngoscopy via a flexible nasendoscope, conducted by a laryngologist, is considered the optimal diagnostic method and involves assessment of secretion management, mucosal integrity, laryngopharyngeal structure, function and sensation. Ideally, videostroboscopy should be conducted to give a detailed view of vocal fold vibration, especially in cases where the larynx appears structurally normal on white light laryngoscopy.[123] Laryngeal electromyography, CT scanning and neck and laryngeal ultrasound can also be used to assess vocal fold movement and RLN function to assist with diagnosis.

Table 1 Documented risk factors for swallowing and laryngeal dysfunction after lung and heart transplantation

Pre-operative	Post-operative	Complications
GERD	Increased duration of intubation	Effusion or empyema
Lower BMI	Increased ICU LOS	Venous thrombosis
Advanced age	Increased hospital LOS	Acute rejection
Tobacco use		
History of cerebrovascular disease		

Abbreviations: LOS, length of stay; BMI, body mass index; GERD, gastro-esophageal reflux disease; ICU, intensive care unit

Oropharyngeal dysphagia

Screening for OPD in all patients within 24 hours of a stroke is now standardized practice as per National Stroke guidelines.[124] However, despite the evidence to support the high rates of PED amongst patients following cardiothoracic transplantation,[12,13,42] there is no similar system in place amongst this patient population.

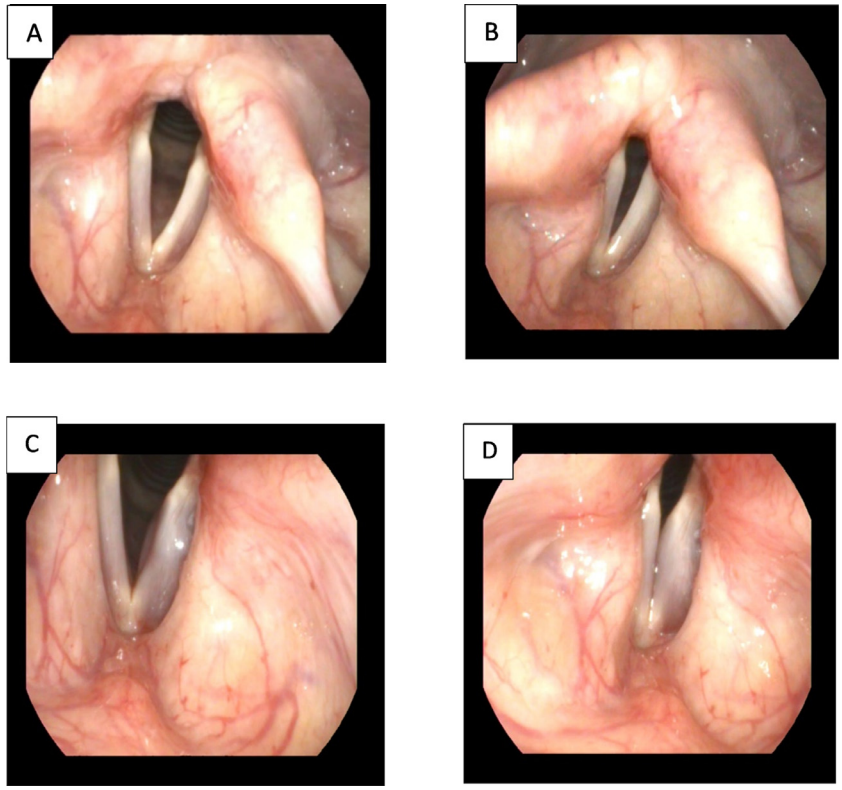
Formal diagnostic assessment is most commonly conducted after extubation via a clinical bedside swallowing examination conducted by a SLP. The assessment is not standardized but typically involves a case history, a cranial nerve examination with a focus on oromuscular structure, function and sensation and oral trials of food and fluid consistencies. Although this is the most frequently used method of assessment, largely for reasons of convenience and ease of accessibility, the sensitivity of this assessment has been reported to be questionable.[125] Silent aspiration is unable to be confirmed via clinical bedside assessment. Following lung transplantation, rates of silent aspiration are reported to be as high as 77% in those diagnosed with OPD[12] and the clinical bedside assessment has been shown to have poor ability to detect aspiration in this population with sensitivity to detect aspiration of 60% and specificity of 49%.[8] Hence, instrumental assessment is strongly recommended to enable accurate diagnosis. This is consistent with the lung transplantation clinical pathway suggested by Baumann and colleagues.[8]

A videofluoroscopic swallow study (VFSS), conducted in the radiology suite, allows radiographic imaging of the dynamic swallow and is considered highly accurate for detection of aspiration.[126-128] There are a number of well accepted rating tools to quantify swallow severity and aspiration during the VFSS[129,130] and the visualisation of aspiration on a VFSS has been linked with an increased risk of pneumonia.[131] However this tool may not be a suitable alternative for an unstable patient in the ICU who cannot leave the unit. Furthermore, VFSS does not allow direct visualization of glottic competence and its interaction with swallowing function.

The optimal tool to investigate both swallowing and laryngeal function simultaneously is the flexible endoscopic evaluation of swallowing (FEES) conducted via nasendoscopy. The patient is required to conduct voice tasks followed by trials of food and fluid consistencies. FEES has a high sensitivity for detection of silent aspiration[132-135] and enables observation of both laryngeal pathology and sensation, and can be conducted at the bedside. This makes FEES a highly usable tool in the ICU following heart and/or lung transplantation.[9,10,112,132] Unfortunately, this method of assessment may not be readily available in all units due to skill mix and/or access to equipment.

Prognosis and management

OPD following transplantation can be of extended duration, with the mean length of time for resolution reported to be up to 91.8 +/- 170 days.[9,12] These figures render a high likelihood for longer term enteral feeding requirements and/or texture diet modifications,



Graphic 2 Pre and post injection laryngoplasty.
Pre injection laryngoplasty — (A) vocal folds in abducted position and (B) vocal folds in adducted position.
Post injection laryngoplasty — (C) vocal folds in abducted position and (D) vocal folds in adducted position.

however, resolution of dysphagia appears to be seen in most patients before discharge with low rates of percutaneous endoscopic gastrostomy insertion.[9]

After surgery, the multidisciplinary team strive to reduce the risks of rejection or dysfunction of the allograft, as well as BOS. Infectious complications are common and while not all are caused by retrograde or anterograde aspiration of food, drink, gastric contents and/or saliva, avoidance of aspiration and protection of the allograft lung is clearly critical.[115] Yet, management of OPD amongst critical care patients is generally underexplored and has not been directly investigated in this transplant population. Dysphagia management generally involves strict oral hygiene regimes, postural changes, texture diet modifications and various therapeutic interventions with newer techniques such as surface electromyography and respiratory muscle strength training being investigated amongst other clinical populations.[136-139]

The trajectory of recovery for laryngotracheal injuries and the associated treatment plan is directly associated with the severity of dysfunction. Dysphonia associated with intubation trauma, demonstrated by inflammation or granuloma on laryngoscopy, may recover spontaneously,[63] however it is generally treated by a SLP in conjunction with a laryngologist. Training in vocal care and voice techniques are provided to attain optimal voice quality whilst minimizing further trauma to the vocal folds to avoid longer term voice misuse.[41] Dysphonia associated with LPR requires medical management via both pharmacological methods and dietary and lifestyle modifications.[111]

The optimal treatment plan for more severe pathology, such as unilateral VFP, varies depending on severity of injury, expected prognosis for recovery, patient co-morbidities, patient willingness to undergo further invasive interventions and local policy at the specific transplant centre.[140] Laryngeal electromyography can be used to assist with prognosis for spontaneous recovery of paralysis, however it is not widely available and is not always definitive.[141] Early injection laryngoplasty, which involves injection of a biocompatible resorbable material to temporarily increase bulk and improve vocal fold closure, can be used short to medium term (see Graphic 2 for images of pre/post laryngoplasty). Laryngeal framework surgery is used in the longer term or where spontaneous recovery is unlikely.[12,14,142] Early injection laryngoplasty has been adopted in some centres based on the concept that compromised glottic function places the patient at higher risk for aspiration related infection. The procedure can be conducted in-office or at the bedside and is considered low risk.[141]

However, the limited available evidence within the heart and lung transplant populations renders argument for direct and early intervention challenging. Seeliger et al[10] recently reported VFP to be transient in 65% of a cohort of lung transplant patients who recovered spontaneously within a period of 6 months and that VFP did not adversely affect graft function, survival or secondary complication rates. However, Atkins et al[12] report that 75% of their cohort required medialization. Early medialization via reabsorbable implant has been suggested to reduce the need for later

more permanent surgical intervention, (e.g., thyroplasty),[143,144] reduce length of stay and pulmonary complications[145] and enable earlier resumption of an oral diet.[146] Earlier injection laryngoplasty is also known to be associated with improvement in long term emotional and social functioning and mental health[144,147] and the accepted consensus in the laryngology literature is that it improves quality of life and patient outcomes whilst waiting for potential recovery of VFP.[148-151] Hence, further robust studies within the transplantation field may support the argument for more aggressive VFP management for improved patient outcomes.

Patient outcomes

For those patients diagnosed with OPD and/or dysphonia after transplantation, the literature suggests an increased risk for a prolonged and complicated hospital admission. Increased hospital length of stay,[9,12] readmissions to ICU,[42] and increased ICU length of stay[9,42] have been reported. The exact nature of these associations has not yet been explored, however the contribution of factors such as critical illness weakness and extended duration of intubation are likely to play a large role as previously discussed. Post-operative complications such as effusion/empyemas, venous thromboses and acute rejection have also been reported to be increased amongst patients with OPD and dysphonia.[12] However, there are conflicting results in the literature. Seeliger and colleagues reported that amongst their large cohort of patients following lung transplantation, there was no inferior rates of 3 year graft survival and CLAD survival in those patients with VFP vs no VFP.[10]

The association between repetitive aspiration of gastroduodenal contents secondary to GERD and the development of BOS, has been well explored in the literature.[108,109,115,152] Current data does not support any association between OPD and dysphonia and BOS.[10,11] However, given the known relationship between GERD and BOS, it appears a strong biological plausibility that recurrent aspiration during the pharyngeal phase of swallowing is also likely to be associated with airway epithelial injury and negative impact on longer term graft function; hence the need for further research in this area.

Conclusions

Evidence of high rates of OPD and dysphonia following heart and/or lung transplantation are now beginning to be reported. This review is the first to identify the potential etiology for these complications and their multifactorial nature in this high risk, immunosuppressed population. This inherent complexity may explain the paucity of robust data to direct clinicians as to the optimal assessment and management approaches. To our knowledge there are no prospective studies to date assessing pre- and post-operative voice and swallowing function. Pre-surgical assessment would allow identification of patients who may be at high risk during and following transplantation and also enable the true incidence of OPD and dysphonia to be determined. Information regarding pre and post-operative risk factors for OPD and dysphonia is scant and conflicting and hence clinicians have limited evidence for early identification to optimize outcomes and minimize secondary complications. These points raise further questions as to the best assessment approach including the need for laryngoscopic assessment of function as a part of the transplantation workup process, accurate identification of those at high risk from pre- and post-operative factors such as respiratory function, intubation duration, reflux status, muscle strength and length of stay, and necessity for routine screening following transplantation. Treatment pathways for voice and swallowing disorders in this population where multiple organ systems are contributing to dysfunction, are not established, and the value of aggressive management of VFP through early intervention to minimize secondary complications is not known. Further research is required to inform the development of a comprehensive best practice protocol, which would be an advancement in understanding for the multidisciplinary team, enabling effective collaboration to reduce aspiration risk and optimize quality of life for the transplant population.

Author contributions

Rebecca Black: Primary author responsible for concept of the manuscript, literature review, writing and editing. Daniel Novakovic: Provision of expert opinion in regard to laryngeal complications and management, graphics, editing. Marshall Plit: Provision of expert opinion in regard to lung transplantation content, editing. Anna Miles: Provision of expert opinion in regard to speech pathology management, editing. Peter MacDonald: Provision of expert opinion in regard to cardiac transplantation, editing. Catherine Madill: Concept of the manuscript in conjunction with the primary author, extensive contributions to writing and editing.

Disclosure statement

The authors have no conflict of interest to declare. This work was conducted at St Vincent's hospital, Sydney and was partially funded from the trust funds of the department of thoracic medicine. The production of the manuscript was supported by the Dr Liang voice programme at the University of Sydney.

References

1. Maurer JR, Tullis DE, Grossman RF, Vellend H, Winton TL, Patterson GA. Infectious complications following isolated lung transplantation. Chest 1992;101:1056-9. https://doi.org/10.1378/chest.101.4.1056.
2. Speich R, Wim van der B. Epidemiology and management of infections after lung transplantation. Clin Infect Dis 2001;33(Supplement 1):S58-65.
3. Cristobo Sáinz P, Lage Gallé E, Sobrino Márquez M, et al. Early mortality after cardiac transplantation: comparison of demographic, clinical, biological and surgical variables. Transplant Proc 2012;44:2111-2. https://doi.org/10.1016/j.transproceed.2012.07.088.

4. Arango Tomas E, Quero Rios MI, Robles Arista JC, et al. Postoperative complications in the intensive care unit following lung transplantation in adults: results in University Hospital Reina Sofia. Transplant Proc 2012;44:2663-5. https://doi.org/10.1016/j.transproceed.2012.09.069.
5. Hoy S, Frisbee J. Common postoperative heart transplant complications. Crit Care Nurs Q 2018;41:383-8. https://doi.org/10.1097/CNQ.0000000000000224.
6. Tejwani V, Panchabhai TS, Kotloff RM, Mehta AC. Complications of lung transplantation. Chest 2016;149:1535-45. https://doi.org/10.1016/j.chest.2015.12.019.
7. Chan EGMD, Bianco VDOMPH, Richards TP, et al. The ripple effect of a complication in lung transplantation: Evidence for increased long-term survival risk. J Thorac Cardiovasc Surg 2016;151:1171-80. https://doi.org/10.1016/j.jtcvs.2015.11.058.
8. Baumann B, Byers S, Wasserman-Wincko T, et al. Postoperative swallowing assessment after lung transplantation. Ann Thorac Surg 2017;104:308-12. https://doi.org/10.1016/j.athoracsur.2017.01.080.
9. Miles A, Barua S, McLellan N, Brkic L. Dysphagia and medicine regimes in patients following lung transplant surgery: a retrospective review. Int J Speech Lang Pathol 2020: 1-10. https://doi.org/10.1080/17549507.2020.1807051. ahead-of-print(ahead-of-print).
10. Seeliger B, Drick N, Avsar M, et al. Risk factors and outcomes of vocal cord paralysis after lung transplantation − a retrospective cohort study. Transpl Int 2019;32:626-34. https://doi.org/10.1111/tri.13402.
11. Atkins BZ, Petersen RP, Daneshmand MA, Turek JW, Lin SS, Davis RD Jr.. Impact of oropharyngeal dysphagia on long-term outcomes of lung transplantation. Ann Thorac Surg 2010;90:1622-8. https://doi.org/10.1016/j.athoracsur.2010.06.089.
12. Atkins BZ, Trachtenberg MS, Prince-Petersen R, et al. Assessing oropharyngeal dysphagia after lung transplantation: altered swallowing mechanisms and increased morbidity. J Heart Lung Transplant 2007;26:1144-8. https://doi.org/10.1016/j.healun.2007.07.038.
13. Black R, McCabe P, Glanville A, Bogaardt H, Macdonald P, Madill C. Oropharyngeal dysphagia and laryngeal dysfunction after lung and heart transplantation: a systematic review. Disabil Rehabil 2019: 1-10. https://doi.org/10.1080/09638288.2018.1552326.
14. de La Rosa A, Aguilar J, Barbu A, Chang D, Kobashigawa J. Uniqueness of laryngeal nerve injury following heart transplantation. J Heart Lung Transplant 2020;39. https://doi.org/10.1016/j.healun.2020.01.617. S280-S280.
15. Ekberg O, Hamdy S, Woisard V, Wuttge−Hannig A, Ortega P. Social and psychological burden of dysphagia: its impact on diagnosis and treatment journal article Dysphagia 2002;17:139-46. https://doi.org/10.1007/s00455-001-0113-5.
16. Smithard D, O'Neill P, Park C, Morris J, Wyatt R, Martin D. Complications and outcome after acute stroke: does dysphagia matter? Stroke 1996;27:1200-4.
17. Altman KW, Yu G, Schaefer SD. Consequence of dysphagia in the hospitalized patient: impact on prognosis and hospital resources. Arch Otolaryngol Head Neck Surg 2010;136:784-9. https://doi.org/10.1001/archoto.2010.129.
18. Ohta N, Kuratani T, Hagihira S, Kazumi K-I, Kaneko M, Mori T. Vocal cord paralysis after aortic arch surgery: predictors and clinical outcome. J Vasc Surg 2006;43:721-8.
19. Lodewyks CL, White CW, Bay G, et al. Vocal cord paralysis after thoracic aortic surgery: incidence and impact on clinical outcomes. Ann Thorac Surg 2015;100:54-8. https://doi.org/10.1016/j.athoracsur.2015.02.021.
20. Taenaka CH, Shibata CS, Okitsu CK, et al. Perioperative factors related to the severity of vocal cord paralysis after thoracic cardiovascular surgery: a retrospective review. Eur J Anaesthesiol 2017;34:425-31. https://doi.org/10.1097/EJA.0000000000000648.
21. Nixon I, Ramsay S, Mackenzie K. Vocal function following discharge from intensive care. J Laryngol Otol 2010;124:515-9. https://doi.org/10.1017/S0022215109992556.
22. Spector BC, Netterville JL, Billante C, Clary J, Reinisch L, Smith TL. Quality-of-life assessment in patients with unilateral vocal cord paralysis. Otolaryngol Head Neck Surg 2001;125:176-82. https://doi.org/10.1067/mhn.2001.117714.
23. Beer A, Reed RM, Bölükbas S, et al. Mechanical ventilation after lung transplantation. An international survey of practices and preferences. Ann Am Thorac Soc 2014;11:546-53. https://doi.org/10.1513/AnnalsATS.201312-419OC.
24. Hadem J, Gottlieb J, Seifert D, et al. Prolonged mechanical ventilation after lung transplantation—a single-center study. Am J Transplant 2016;16:1579-87. https://doi.org/10.1111/ajt.13632.
25. Padia SA, Borja MC, Orens JB, Yang SC, Jhaveri RM, Conte JV. Tracheostomy following lung transplantation predictors and outcomes: tracheostomy following lung transplantation. Am J Transplant 2003;3:891-5. https://doi.org/10.1034/j.1600-6143.2003.00170.x.
26. Miyoshi R, Chen-Yoshikawa TF, Hamaji M, et al. Effect of early tracheostomy on clinical outcomes in critically ill lung transplant recipients. Gen Thorac Cardiovas Surg 2018;66:529-36. https://doi.org/10.1007/s11748-018-0949-3.
27. Murty GE, Smith MC. Recurrent laryngeal nerve palsy following heart-lung transplantation: three cases of vocal cord augmentation in the acute phase. Case reports. *J Laryngol Otol*. 103:968-9.
28. Gamez J, Salvado M, Martinez-de La Ossa A, et al. Influence of early neurological complications on clinical outcome following lung transplant. PLoS One 2017;12:e0174092. https://doi.org/10.1371/journal.pone.0174092.
29. Davis CS, Shankaran V, Kovacs EJ, et al. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. Surgery 2010;148:737-45. https://doi.org/10.1016/j.surg.2010.07.011.
30. Young LR, Hadjiliadis D, Davis RD, Palmer SM. LUng transplantation exacerbates gastroesophageal reflux disease*. Chest 2003;124:1689-93. https://doi.org/10.1378/chest.124.5.1689.
31. D'ovidio F, Keshavjee S. Gastroesophageal Reflux and Lung Transplantation. Melbourne, Australia: Blackwell Publishing Asia; 2006:315-20.
32. Jha SR, Hannu MK, Chang S, et al. The prevalence and prognostic significance of frailty in patients with advanced heart failure referred for heart transplantation. Transplantation 2016;100:429-36. https://doi.org/10.1097/tp.0000000000000991.
33. Jha SR, Hannu MK, Newton PJ, et al. Reversibility of frailty after bridge-to-transplant ventricular assist device implantation or heart transplantation. Transplantation direct 2017;3. https://doi.org/10.1097/txd.0000000000000690. e167-e167.
34. Gross RD, Atwood CW Jr., Ross SB, Olszewski JW, Eichhorn KA. The coordination of breathing and swallowing in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;179:559-65. https://doi.org/10.1164/rccm.200807-1139OC.
35. Martin-Harris B, Brodsky MB, Price CC, Michel Y, Walters B. Temporal coordination of pharyngeal and laryngeal dynamics with breathing during swallowing: single liquid swallows. J Appl Physiol (1985) 2003;94:1735-43. https://doi.org/10.1152/japplphysiol.00806.2002.
36. Martin-Harris B, Brodsky MB, Michel Y, Ford CL, Walters B, Heffner J. Breathing and swallowing dynamics across the adult lifespan. Arch Otolaryngol Head Neck Surg 2005;131:762-70. https://doi.org/10.1001/archotol.131.9.762.
37. Langmore SE. Endoscopic Evaluation and Treatment of Swallowing Disorders. Thieme; 2001.
38. Macht M, Wimbish T, Bodine C, Moss M. ICU-acquired swallowing disorders. Crit Care Med 2013;41:2396-405. https://doi.org/10.1097/CCM.0b013e31829caf33.
39. Boone DR. The Voice and Voice Therapy. Ninth edition Pearson Education Inc.; 2013 ed. Allyn & Bacon communication sciences and disorders series.
40. Sataloff RT, Heman-Ackah YD, Hawkshaw MJ. Clinical anatomy and physiology of the voice. Otolaryngol Clin North Am 2007;40:909-29. https://doi.org/10.1016/j.otc.2007.05.002.
41. Robert TS. The human voice. Sci Am 1992;267:108. https://doi.org/10.1038/scientificamerican1292-108.

42. Black RJ, Bogaardt H, McCabe P, Glanville AR, Macdonald P, Madill C. Clinical predictors for oropharyngeal dysphagia and laryngeal dysfunction after lung and heart transplantation. Int J Lang Commun Disord 2019;54:894-901. https://doi.org/10.1111/1460-6984.12492.
43. Shaker R, Li Q, Ren J, et al. Coordination of deglutition and phases of respiration: effect of aging, tachypnea, bolus volume, and chronic obstructive pulmonary disease. Am J Physiol Gastrointest Liver Physiol 1992;263:G750-5. https://doi.org/10.1152/ajpgi.1992.263.5.G750.
44. Nilsson H, Ekberg O, Bulow M, Hindfelt B. Assessment of respiration during video fluoroscopy of dysphagic patients. Acad Radiol 1997;4:503-7. https://doi.org/10.1016/S1076-6332(97)80237-1.
45. Brodsky M, Levy M, Jedlanek E, et al. Laryngeal injury and upper airway symptoms after oral endotracheal intubation with mechanical ventilation during critical care. Crit Care Med 2018;46:2010-7. https://doi.org/10.1097/CCM.0000000000003368.
46. Sanuki T, Mishima G, Kiriishi K, et al. Effect of nasal high-flow oxygen therapy on the swallowing reflex: an in vivo volunteer study. Clin Oral Investig 2017;21:915-20. https://doi.org/10.1007/s00784-016-1822-3.
47. Oomagari M, Fujishima I, Katagiri N, et al. Swallowing function during high-flow nasal cannula therapy. Eur Respir J 2015;46(suppl 59):PA4199. https://doi.org/10.1183/13993003.congress-2015.PA4199.
48. Thawanaphong S, Kitisomprayoonkul W, Pongpipatpaiboon K, Kongpolprom N. Electromyographic swallowing study during high flow oxygen therapy compared with low flow oxygen therapy in post-extubated patients. Eur Respir J 2019;54(suppl 63):PA4021. https://doi.org/10.1183/13993003.congress-2019.PA4021.
49. Tong JY, Sataloff RT. Respiratory function and voice: the role for airflow measures. J Voice 2020. https://doi.org/10.1016/j.jvoice.2020.07.019.
50. Enas Elsayed M, Riham Ali El M. Voice changes in patients with chronic obstructive pulmonary disease. Egypt J Chest Dis Tuber 2014;63:561-7. https://doi.org/10.1016/j.ejcdt.2014.03.006.
51. Saeed A, Riad N, Osman N, Nabil Khattab A, Mohammed S. Study of voice disorders in patients with bronchial asthma and chronic obstructive pulmonary disease. Egypt J Bronchology 2018;12:20-6. https://doi.org/10.4103/ejb.ejb_34_17.
52. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. Can J Surg 2009;52:119-24.
53. Bordon A, Bokhari R, Sperry J, Testa Dt, Feinstein A, Ghaemmaghami V. Swallowing dysfunction after prolonged intubation: analysis of risk factors in trauma patients. Am J Surg 2011;202:679-83.
54. Brodsky MB, Gellar JE, Dinglas VD, et al. Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. J Crit Care 2014;29:574-9. https://doi.org/10.1016/j.jcrc.2014.02.015.
55. Hogue CW, Lappas GD, Creswell LL, et al. Swallowing dysfunction after cardiac operations: associated adverse outcomes and risk factors including intraoperative transesophageal echocardiography. J Thorac Cardiovasc Surg 1995;110:517-22. https://doi.org/10.1016/S0022-5223(95)70249-0.
56. Kwok AM, Davis JW, Cagle KM, Sue LP, Kaups KL. Post-extubation dysphagia in trauma patients: it's hard to swallow. Am J Surg 2013;206:924-8. https://doi.org/10.1016/j.amjsurg.2013.08.010.
57. Sue RD, Susanto I. Long-term complications of artificial airways. Clin Chest Med 2003;24:457-71. https://doi.org/10.1016/S0272-5231(03)00048-0.
58. Colice GL, Stukel TA, Dain B. Laryngeal complications of prolonged intubation. Chest 1989;96:877-84.
59. Kastanos N, Miro R, Perez A, Mir A, Agusti-Vidal A. Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long term study. Crit Care Med 1983;11.
60. Scheel R, Pisegna J, McNally E, Noordzij J, Langmore S. Endoscopic assessment of swallowing after prolonged intubation in the ICU setting. Ann Otol Rhinol Laryngol 2015;125:43-52. https://doi.org/10.1177/0003489415596755.
61. Benjamin B. Prolonged intubation injuries of the larynx: endoscopic diagnosis, classification, and treatment. Ann Otol Rhinol Laryngol 2018;127:492-507. https://doi.org/10.1177/0003489418790348.
62. Zuercher P, Moret C, Dziewas R, Schefold J. Dysphagia in the intensive care unit: epidemiology, mechanisms, and clinical management. Crit Care 2019;23. https://doi.org/10.1186/s13054-019-2400-2. 103-undefined.
63. Ganzel TM, Brohm J, Nechtman CM, Ganzel BL, Klein JB, Gray LA Jr. Otolaryngologic problems in cardiac transplant patients. Laryngoscope 1989;99:158-61.
64. Whited RE. A prospective study of laryngotracheal sequelae in long-term intubation. Laryngoscope 1984;94:367-77. https://doi.org/10.1288/00005537-198403000-00014.
65. Macht M, Wimbish T, Clark BJ, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. Crit Care 2011;15:R231. https://doi.org/10.1186/cc10472.
66. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest 2010;137:665-73. https://doi.org/10.1378/chest.09-1823.
67. Ferraris VA, Ferraris SP, Moritz DM, Welch S. Oropharyngeal dysphagia after cardiac operations. Ann Thorac Surg 2001;71:1792-6. https://doi.org/10.1016/S0003-4975(01)02640-6.
68. Schefold CJ, Berger MD, Zürcher MP, et al. Dysphagia in mechanically ventilated ICU patients (DYnAMICS): a prospective observational trial. Crit Care Med 2017;45:2061-9. https://doi.org/10.1097/CCM.0000000000002765.
69. Smithard DG, Smeeton NC, Wolfe CDA. Long-term outcome after stroke: does dysphagia matter? Age Ageing 2007;36:90-4.
70. Tabaee A, Murry T, Zschommler A, Desloge RB. Flexible endoscopic evaluation of swallowing with sensory testing in patients with unilateral vocal fold immobility: incidence and pathophysiology of aspiration. Laryngoscope 2005;115:565-9. https://doi.org/10.1097/01.mlg.0000161358.20450.12.
71. De Larminat V, Montravers P, Dureuil B, Desmonts J-M. Alteration in swallowing reflex after extubation in intensive care unit patients. Crit Care Med 1995;23:486-90.
72. Schefold J, Berger D, Zürcher P, et al. Dysphagia in mechanically ventilated ICU patients (DYnAMICS). Crit Care Med 2017;45:2061-9. https://doi.org/10.1097/CCM.0000000000002765.
73. Kikura M, Suzuki K, Itagaki T, Takada T, Sato S. Age and comorbidity as risk factors for vocal cord paralysis associated with tracheal intubation. Br J Anaesth 2007;98:524-30.
74. Ajemian MS, Nirmul GB, Anderson MT, Zirlen DM, Kwasnik EM. Routine fiberoptic endoscopic evaluation of swallowing following prolonged intubation: implications for management. Arch Surg 2001;136:434-7. https://doi.org/10.1001/archsurg.136.4.434.
75. Barquist. Postextubation fiberoptic endoscopic evaluation of swallowing after intubation. Crit Care Med 2001;29:1710-3.
76. Skoretz SA, Yau TM, Ivanov J, Granton JT, Martino R. Dysphagia and associated risk factors following extubation in cardiovascular surgical patients. Dysphagia 2014;29:647-54. https://doi.org/10.1007/s00455-014-9555-4.
77. Raut MS, Maheshwari A, Joshi R, et al. Vocal cord paralysis after cardiac surgery and interventions: a review of possible etiologies. J Cardiothorac Vasc Anesth 2016;30:1661-7. https://doi.org/10.1053/j.jvca.2016.08.002.
78. Dimarakis I, Protopapas AD. Vocal cord palsy as a complication of adult cardiac surgery: surgical correlations and analysis. Eur J Cardiothorac Surg 2004;26:773-5. https://doi.org/10.1016/j.ejcts.2004.06.003.
79. Hamdan AL, Moukarbel RV, Farhat F, Obeid M. Vocal cord paralysis after open-heart surgery. Eur J Cardiothorac Surg 2002;21:671-4.
80. Joo D, Duarte VM, Ghadiali MT, Chhetri DK. Recovery of vocal fold paralysis after cardiovascular surgery. Laryngoscope 2009;119:1435-8. https://doi.org/10.1002/lary.20525.

81. DiLisio RP, Mazzeffi MA, Bodian CA, Fischer GW. Vocal cord paralysis after aortic surgery. J Cardiothorac Vasc Anesth 2013;27:522-7. https://doi.org/10.1053/j.jvca.2012.09.011.
82. Itagaki T, Kikura M, Sato S. Incidence and risk factors of postoperative vocal cord paralysis in 987 patients after cardiovascular surgery. Ann Thorac Surg 2007;83:2147-52.
83. Huddleston CB, Richey SR. Heart-lung transplantation. J Thorac Dis 2014;6:1150-8. https://doi.org/10.3978/j.issn.2072-1439.2014.05.11.
84. Jung A, Schramm J. How to reduce recurrent laryngeal nerve palsy in anterior cervical spine surgery: a prospective observational study. Neurosurgery 2010;67:10-5. https://doi.org/10.1227/01.Neu.0000370203.26164.24.
85. Jeannon JP, Orabi AA, Bruch GA, Abdalsalam HA, Simo R. Diagnosis of recurrent laryngeal nerve palsy after thyroidectomy: a systematic review. Int J Clin Pract (Esher) 2009;63:624-9. https://doi.org/10.1111/j.1742-1241.2008.01875.x.
86. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014;370:1626. https://doi.org/10.1056/NEJMra1209390.
87. Jolley SE, Bunnell AE, Hough CL. ICU-Acquired weakness. Chest 2016;150:1129-40. https://doi.org/10.1016/j.chest.2016.03.045.
88. Judemann K, Lunz D, Zausig YA, Graf BM, Zink W. Intensive care unit-acquired weakness in the critically ill. Anaesthesist 2011;60:887-901. https://doi.org/10.1007/s00101-011-1951-7.
89. Thille AW, Boissier F, Muller M, et al. Role of ICU-acquired weakness on extubation outcome among patients at high risk of reintubation.(intensive care unit)(Report). Crit Care 2020;24. https://doi.org/10.1186/s13054-020-2807-9.
90. Thille WA, Boissier WF, Ben Ghezala WH, Razazi WK, Mekontso-Dessap WA, Brun-Buisson WC. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study*. Crit Care Med 2015;43:613-20. https://doi.org/10.1097/CCM.0000000000000748.
91. Beuret P, Roux C, Auclair A, Nourdine K, Kaaki M, Carton M-J. Interest of an objective evaluation of cough during weaning from mechanical ventilation. Intensive Care Med 2009;35:1090-3. https://doi.org/10.1007/s00134-009-1404-9.
92. Bianchi C, Baiardi P, Khirani S, Cantarella G. Cough peak flow as a predictor of pulmonary morbidity in patients with dysphagia. Am J Phys Med Rehabil 2012;91:783-8. https://doi.org/10.1097/PHM.0b013e3182556701.
93. Kulnik ST, Birring SS, Hodsoll J, Moxham J, Rafferty GF, Kalra L. Higher cough flow is associated with lower risk of pneumonia in acute stroke. Thorax 2016. https://doi.org/10.1136/thoraxjnl-2015-207810.
94. Hafner G, Neuhuber A, Hirtenfelder S, Schmedler B, Eckel HE. Fiberoptic endoscopic evaluation of swallowing in intensive care unit patients. Eur Arch Otorhinolaryngol 2008;265:441-6. https://doi.org/10.1007/s00405-007-0507-6.
95. Ponfick M, Linden R, Nowak DA. Dysphagia—a common, transient symptom in critical illness polyneuropathy: a fiberoptic endoscopic evaluation of swallowing study*. Crit Care Med 2015;43:365-72. https://doi.org/10.1097/CCM.0000000000000705.
96. Thomas S, Sauter W, Starrost U, Pohl M, Mehrholz J. Regaining water swallowing function in the rehabilitation of critically ill patients with intensive-care-unit acquired muscle weakness. Disabil Rehabil 2018;40:1494-500. https://doi.org/10.1080/09638288.2017.1300341.
97. Mirzakhani JH, Williams JJ-N, Mello JJ, et al. Muscle weakness predicts pharyngeal dysfunction and symptomatic aspiration in long-term ventilated patients. Anesthesiology 2013;119:389-97. https://doi.org/10.1097/ALN.0b013e31829373fe.
98. Aids to the Examination of the Peripheral Nervous System. Memorandum /Medical Research Council; 1976 no 45. H.M.S.O..
99. Paternostro-Sluga T, Grim-Stieger M, Posch M, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med 2008;40:665-71. https://doi.org/10.2340/16501977-0235.
100. Sweet PM, Herbella AMF, Leard GL, et al. The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. Ann Surg 2006;244:491-7. https://doi.org/10.1097/01.sla.0000237757.49687.03.
101. Cantu E, Appel JZ, Hartwig MG, et al. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg 2004;78:1142-51. https://doi.org/10.1016/j.athoracsur.2004.04.044.
102. D'Ovidio F, Singer LG, Hadjiliadis D, et al. Prevalence of gastroesophageal reflux in end-stage lung disease candidates for lung transplant. Ann Thorac Surg 2005;80:1254-60. https://doi.org/10.1016/j.athoracsur.2005.03.106.
103. Tobin RW, Pope CE, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;158:1804-8. https://doi.org/10.1164/ajrccm.158.6.9804105.
104. Yates RB, Pellegrini CA, Oelschlager BK. Gastroesophageal reflux and esophageal dysmotility in patients undergoing evaluation for lung transplantation: assessment, evaluation, and management. In: Raghu G, Carbone RG, eds. Lung Transplantation: Evolving Knowledge and New Horizons, Springer International Publishing; 2018:279-99.
105. Reid KR, McKenzie FN, Menkis AH, et al. Importance of chronic aspiration in recipients of heart-lung transplants. The Lancet (British edition) 1990;336:206-8. https://doi.org/10.1016/0140-6736(90)91734-R.
106. Hathorn KE, Chan WW, Lo W-K. Role of gastroesophageal reflux disease in lung transplantation. World J Transplant 2017;7:103. https://doi.org/10.5500/wjt.v7.i2.103.
107. King BJ, Iyer H, Leidi AA, Carby MR. Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. J Heart Lung Transplant 2009;28:870-5. https://doi.org/10.1016/j.healun.2009.05.040.
108. Gulack BC, Meza JM, Lin SS, Hartwig MG, Davis RD. Reflux and allograft dysfunction: is there a connection? Thorac Surg Clin 2015;25:97-105. https://doi.org/10.1016/j.thorsurg.2014.09.006.
109. Hartwig GM, Davis DR. Gastroesophageal reflux disease-induced aspiration injury following lung transplantation. Curr Opin Organ Transplant 2012;17:474-8. https://doi.org/10.1097/MOT.0-b013e328357f84f.
110. Wood R. Esophageal dysmotility, gastro-esophageal reflux disease, and lung transplantation: what is the evidence? Curr Gastroenterol Rep 2015;17:1-8. https://doi.org/10.1007/s11894-015-0474-9.
111. Martinucci I, de Bortoli N, Savarino E, et al. Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis 2013;4:287-301. https://doi.org/10.1177/2040622313503485.
112. Aviv JE, Liu H, Kaplan ST, Parides M, Close LG. Laryngopharyngeal sensory deficits in patients with laryngopharyngeal reflux and dysphagia. Ann Otol Rhinol Laryngol 2000;109:1000-6. https://doi.org/10.1177/000348940010901103.
113. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101(4 Pt 2 Suppl 53):1-78. https://doi.org/10.1002/lary.1991.101.s53.1.
114. Posner S, Zheng J, Wood RK, et al. Gastroesophageal reflux symptoms are not sufficient to guide esophageal function testing in lung transplant candidates. Dis Esophagus 2018;31. https://doi.org/10.1093/dote/dox157.
115. Patti MG, Vela MF, Odell DD, Richter JE, Fisichella PM, Vaezi MF. The intersection of GERD, aspiration, and lung transplantation. J Laparoendosc Adv Surg Tech 2016;26:51-505. https://doi.org/10.1089/lap.2016.0170.
116. Lidor AO, Ensor CR, Sheer AJ, Orens JB, Clarke JO, McDyer JF. Domperidone for delayed gastric emptying in lung transplant recipients with and without gastroesophageal reflux. Prog Transplant (Aliso Viejo, Calif) 2014;24:27-32. https://doi.org/10.7182/pit2014823.
117. Hoppo T, Jarido V, Pennathur A, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and

end-stage lung disease before and after lung transplantation. Arch Surg (Chicago 1960) 2011;146:1041-7. https://doi.org/10.1001/archsurg.2011.216.
118. Leder SB, Suiter DM, Lisitano Warner H. Answering orientation questions and following single-step verbal commands: effect on aspiration status. Dysphagia 2009;24:290-5. https://doi.org/10.1007/s00455-008-9204-x.
119. Berkowitz N, Schulman LL, McGregor C, Markowitz D. Gastroparesis after lung transplantation: potential role in postoperative respiratory complications. Chest 1995;108:1602-7.
120. Carl L, Johnson P. Drugs and dysphagia. Perspect Swallowing Swallowing Dis (Dysphagia) 2008;17:143-8.
121. Eckel FC, Boone DR. The S/Z ratio as an indicator of laryngeal pathology. J Speech Hear Disord 1981;46:147-9. https://doi.org/10.1044/jshd.4602.147.
122. Van Der Meer G, Ferreira Y, Loock JW. The S/Z ratio: a simple and reliable clinical method of evaluating laryngeal function in patients after intubation. J Crit Care 2010;25:489-92. https://doi.org/10.1016/j.jcrc.2009.11.009.
123. Patel RR, Awan SN, Barkmeier-Kraemer J, et al. Recommended protocols for instrumental assessment of voice: American speech-language-hearing association expert panel to develop a protocol for instrumental assessment of vocal function. Am J Speech Lang Pathol 2018;27:887-905. https://doi.org/10.1044/2018_AJSLP-17-0009.
124. Clinical Guidelines for Stroke Managment. Stroke foundation; 2020.
125. McCullough GH, Wertz RT, Rosenbek JC. Sensitivity and specificity of clinical/bedside examination signs for detecting aspiration in adults subsequent to stroke. J Commun Disord 2001;34:55-72. https://doi.org/10.1016/S0021-9924(00)00041-1.
126. Scott A, Perry A, Bench J. A study of interrater reliability when using videofluoroscopy as an assessment of swallowing. Dysphagia 1998;13:223-7. https://doi.org/10.1007/PL00009576.
127. Stoeckli SJ, Huisman TAGM, Seifert BAGM, Martin−Harris BJW. Interrater reliability of videofluoroscopic swallow evaluation. Dysphagia 2003;18:53-7. https://doi.org/10.1007/s00455-002-0085-0.
128. McCullough GH, Wertz RT, Rosenbek JC, Mills RH, Webb WG, Ross KB. Inter- and intrajudge reliability for videofluoroscopic swallowing evaluation measures. Dysphagia 2001;16:110-8. https://doi.org/10.1007/PL00021291.
129. Rosenbek J, Robbins J, Roecker E, Coyle J, Wood J. A penetration-aspiration scale. Dysphagia 1996;11:93-8. https://doi.org/10.1007/BF00417897.
130. Hutcheson KA, Barrow MP, Barringer DA, et al. Dynamic imaging grade of swallowing toxicity (DIGEST): scale development and validation. Cancer 2017;123:62-70. https://doi.org/10.1002/cncr.30283.
131. Pikus L, Levine MS, Yang Y-X, et al. Videofluoroscopic studies of swallowing dysfunction and the relative risk of pneumonia. AJR Am J Roentgenol 2003;180:1613-6. https://doi.org/10.2214/ajr.180.6.1801613.
132. Colodny N. Interjudge and intrajudge reliabilities in fiberoptic endoscopic evaluation of swallowing (Fees ®) using the penetration−aspiration scale: a replication study. Dysphagia 2002;17:308-15. https://doi.org/10.1007/s00455-002-0073-4.
133. Langmore SE, Schatz K, Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. Ann Otol Rhinol Laryngol 1991;100:678-81. https://doi.org/10.1177/000348949110000815.
134. Giraldo-Cadavid LF, Leal-Leaño LR, Leon-Basantes GA, et al. Accuracy of endoscopic and videofluoroscopic evaluations of swallowing for oropharyngeal dysphagia. Laryngoscope 2017;127:2002-10. https://doi.org/10.1002/lary.26419.
135. Madden C, Fenton J, Hughes J, Timon C. Comparison between videofluoroscopy and milk-swallow endoscopy in the assessment of swallowing function. Clin Otolaryngol 2000;25:504-6. https://doi.org/10.1046/j.1365-2273.2000.00385.x.
136. Mancopes R, Smaoui S, Steele C. Effects of expiratory muscle strength training on videofluoroscopic measures of swallowing: a systematic review. Am J Speech Lang Pathol (Online) 2020;29:335-56. https://doi.org/10.1044/2019_AJSLP-19-00107.
137. Troche MS. Respiratory muscle strength training for the management of airway protective deficits. Perspect Swallowing Swallowing Dis (Dysphagia) 2015;24:58. https://doi.org/10.1044/sasd24.2.58.
138. Hutcheson KA, Barrow MP, Plowman EK, et al. Expiratory muscle strength training for radiation-associated aspiration after head and neck cancer: a case series. Laryngoscope 2018;128:1044. https://doi.org/10.1002/lary.26845.
139. Stepp CE. Surface electromyography for speech and swallowing systems: measurement, analysis, and interpretation. J Speech, Lang Hear Res (Online) 2012;55:1232-1246A. https://doi.org/10.1044/1092-4388(2011/11-0214).
140. Zuniga S, Ebersole B, Jamal N. Inpatient injection laryngoplasty for vocal fold immobility: when is it really necessary? Am J Otolaryngol 2017;38:222-5. https://doi.org/10.1016/j.amjoto.2017.01.016.
141. Amin MR, Johns MM, eds. Decision Making in Vocal Fold Paralysis A Guide to Clinical Management, 1st ed., Springer International Publishing; 2019. 2019. ed..
142. Hendriks T, Wormald R. Improvement in lung function following medialisation thyroplasty in a postbilateral lung transplant patient. BMJ Case Rep 2018. https://doi.org/10.1136/bcr-2018-225998.
143. Friedman AD, Burns JA, Heaton JT, Zeitels SM. Early versus late injection medialization for unilateral vocal cord paralysis. Laryngoscope 2010;120:2042-6. https://doi.org/10.1002/lary.21097.
144. Fang TJ, Pei YC, Li HY, Wong AMK, Chiang HC. Glottal gap as an early predictor for permanent laryngoplasty in unilateral vocal fold paralysis. Laryngoscope 2014;124:2125-30. https://doi.org/10.1002/lary.24689.
145. Chen DW, Price MD, Lemaire SA, Coselli JS, Liou NE, Ongkasuwan J. Early versus late inpatient awake transcervical injection laryngoplasty after thoracic aortic repair. Laryngoscope 2018;128:144-7. https://doi.org/10.1002/lary.26747.
146. Graboyes EM, Bradley JP, Meyers BF, Nussenbaum B. Efficacy and safety of acute injection laryngoplasty for vocal cord paralysis following thoracic surgery. Laryngoscope 2011;121:2406-10. https://doi.org/10.1002/lary.22178.
147. Pei Y-C, Fang T-J, Hsin L-J, Li H-Y, Wong AM. Early hyaluronate injection improves quality of life but not neural recovery in unilateral vocal fold paralysis: an open-label randomized controlled study. Restor Neurol Neurosci 2015;33:121-30. https://doi.org/10.3233/RNN-140439.
148. Vila PM, Bhatt NK, Paniello RC. Early-injection laryngoplasty may lower risk of thyroplasty: a systematic review and meta-analysis. Laryngoscope 2018;128:935-40. https://doi.org/10.1002/lary.26894.
149. Reder L, Bertelsen C, Angajala V, O'Dell K, Fisher L. Hospitalized patients with new-onset vocal fold immobility warrant inpatient injection laryngoplasty. Laryngoscope 2021;131:115-20. https://doi.org/10.1002/lary.28606.
150. Sielska-Badurek EM, Sobol M, Jędra K, Rzepakowska A, Osuch-Wójcikiewicz E, Niemczyk K. Injection laryngoplasty as miniinvasive office-based surgery in patients with unilateral vocal fold paralysis - voice quality outcomes. Wideochirurgia i inne techniki mało inwazyjne 2017;12:277-84. https://doi.org/10.5114/wiitm.2017.68868.
151. Mohammed H, Masterson L, Gendy S, Nassif R. Outpatient-based injection laryngoplasty for the management of unilateral vocal fold paralysis − clinical outcomes from a UK centre. Clin Otolaryngol 2016;41:341-6. https://doi.org/10.1111/coa.12516.
152. Hartwig MG, Appel JZ, Li B, et al. Chronic aspiration of gastric fluid accelerates pulmonary allograft dysfunction in a rat model of lung transplantation. J Thorac Cardiovasc Surg 2006;131:209-17. https://doi.org/10.1016/j.jtcvs.2005.06.054.