Laryngotracheal Stenosis: Drug Delivery Approaches and Strategies

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Short Summary (256 character): Laryngotracheal stenosis is a rare but devastating progressive fibrosis resulting in airway narrowing; with limited treatment options. This review discusses drug delivery treatments, highlights administration routes & preclinical biomaterials approaches.

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Abstract

Laryngotracheal stenosis (LTS) refers to narrowing of the airway at the vocal folds, subglottis, or cervical trachea and is observed in adults usually following prolonged intubation, tracheostomy, or trauma. Current understanding of pathophysiology suggests that an auto-feedback loop stemming from the immune response, activates inflammatory pathways, leading to fibroblast proliferation, and excessive extracellular matrix production resulting in fibroplasia and airway stenosis. Airway stenosis and disrupted mucociliary clearance lead to deterioration of upper airway function necessitating medical and, most often, surgical intervention. Oral, intravenous, or locally injected therapeutics can reduce inflammation and fibrosis, yet most cases necessitate endoscopic or open surgical interventions to provide a safe airway. Due to poor anatomical accessibility and lack of novel and tolerable treatment options for patients, targeted local drug administration is necessary to maximize therapeutic efficacy and minimize systemic side-effects remains limited. In this manuscript, currently available therapeutic choices across various interventional drug delivery and administration approaches/models used *in vitro*, *in vivo*, and in clinical cases of LTS treatment are reviewed.

Introduction

Laryngotracheal stenosis (LTS) refers to the narrowing of the airway at the level of the vocal folds, subglottis, or cervical trachea and is generally a result of prolonged intubation, tracheostomy, or iatrogenic or external trauma. Iatrogenic LTS in adults is a late complication of both intubation trauma and the normal course of an intubated patient, following prolonged intubation and/or tracheostomy[1]. The reported LTS incidence rate is as high as 12% in patients who had been intubated for more than 11 days[2-4] and 21% for patients following tracheotomy[5-7], resulting in an annual health care cost of more than $5,000 per patient with intubation-related stenosis[8]. LTS may occur[9] anywhere along the laryngotracheal tract but can best be characterized in four categories: glottic stenosis, posterior glottic stenosis, subglottic stenosis, or tracheal stenosis (**Figure 1A**). Glottic stenosis occurs after severe webbing of the vocal folds or in the setting of bilateral vocal fold immobility secondary to posterior glottic tethering/scarring of the arytenoids and vocal folds or autoimmune disease such as amyloidosis. It results in subsequent narrowing of the glottic opening, which, in adults, is the narrowest portion of the airway. Similarly, posterior glottic stenosis occurs via scarring/fibrosis at the posterior glottis resulting in decreased vocal fold abduction and an overall narrowing of the glottic aperture. Subglottic stenosis, linked to idiopathic etiologies, autoimmune diseases such as granulomatosis with polyangiitis, or prolonged intubation, is narrowing just inferior to the vocal folds but superior or at the level of the inferior border of the cricoid cartilage, the only complete cartilaginous ring of the airway[10]. Below that, in the cervical trachea, tracheal stenosis, most commonly associated with tracheostomy, occurs at either the stoma after the tracheostomy tube has been removed or where the endotracheal tube (ETT) cuff makes contact with the respiratory epithelium of the trachea[11]. In the latter case, the tracheostomy tube pressure generally causes ischemia-induced mucosal necrosis followed by inflammation and scarring[10, 12] (**Figure 1**). Cartilage damage in the tracheal wall has also been observed due to cuff pressure. As a result, cuff pressure measurements intraoperatively and in the critical care unit are employed to minimize tracheal wall injury. The subsequent wound healing process includes inflammation, proliferation, and maturation[13] of fibrotic tissue in the affected site.

Current understanding of underlying aetiology of post-intubation stenosis and the cellular/molecular mechanisms involved in fibrosis and tissue proliferation leading to airway narrowing were recently reviewed by Dorris and colleagues[10]. Briefly, the initial phase of wound healing results in an inflammatory response that attracts inflammatory mediators (leukocytes) and their secretory products such as prostaglandins, interleukins (ILs) 1 and 6, tumor necrosis factor-alpha (TNFα), and initiates transforming growth factor-beta (TGF-β) signaling[13]. The cells involved in the proliferative phase of wound healing include fibroblasts, epithelial cells, and endothelial cells. Within this inflammatory response, macrophage secreted cytokines activate fibroblasts and initiate their differentiation into myofibroblasts, which are prolific at extracellular matrix (ECM) production during wound healing, including a superfamily of collagen and elastin towards new connective tissue formation. An increase in collagen production and ECM deposition induce granulation at the site. In the next phase of wound healing, mature scar tissue is formed due to the conversion of type III to type I collagen; the latter collagen type being highly organized and arranged along the principal stress direction of the contracting wound matrix. This final stage of wound healing is primarily controlled by two main growth factors, namely epidermal growth factor(EGF) and TGF-β1[13]. During LTS onset, the balance between growth factor secretion, cell proliferation, and ECM production in wound healing is disrupted, resulting in hypertrophic

scarring whose growth obstructs the airway[14] while tissue fibrosis, as a response to a positive auto-feedback loop, activates an excessive immune response[13, 15-18] (**Figure 1B**). Further complicating wound healing is the curved tubular structure of the trachea, where scar contracture during fibrosis results in overall airway aperture narrowing. Diseases impairing wound healing and normal immune function, such as diabetes mellitus, can lead to or worsen LTS.

According to the McCaffrey laryngotracheal stenosis classification[19], obstruction caused by LTS has four primary clinical grades. Grade I is scar tissue (less than 1 cm) formation in the subglottis and trachea, whereas the presence of scar tissue (longer than 1 cm) confined within the cricoid ring is classified as Grade II. Evidence of scars in the upper trachea without glottic involvement is Grade III, whereas scar tissue on the vocal folds and fixation or paralysis of one or both vocal folds is considered Grade IV (**Figure 1C**)[1, 19, 20]. After comprehensive assessment and laryngotracheal stenosis classification, patients may undergo a variety of surgical and/or therapeutic interventions. Surgical interventions include tracheotomy[7, 21], airway reconstruction surgery[22], tracheal laser surgery, tracheal dilation[23], placement of a tracheal airway stent[24], or a combination of these procedures. Drug delivery (usually corticosteroids, and various other drug classes are discussed in the following section) by topical application, local injection or systemic administration is used to control further inflammation, to promote healing and stave off further surgery. Pediatric LTS cases require additional attention based on the age and weight of the child and, commonly, associated comorbidities [25]. Subglottic and tracheal stenosis can also be classified by the Meyer-Cotton scale based purely on a categorical scale of tracheal narrowing[26]. This commonly employed clinical scale is useful for how narrow an airway is, but it does not incorporate the length of the stenosis, an important factor in treatment success.

As an adjuvant to surgery, local topical- or injection-administration of therapeutics has shown promise in controlling early inflammation, possible infection, fibroplasia, and restenosis. Therapeutic delivery has been employed after extubation, during surgery, and post-surgery to improve surgical results and control recurrence of stenosis. In addition, therapeutics can be delivered intraoperatively or in the office in awake patients under video-laryngoscopy and tracheoscopy. Although results demonstrate varying efficacy of medications in the treatment of LTS, many pathophysiological parameters impacting efficacy remain unknown[10].

Classes of Therapeutics

Current approaches to LTS management can be categorized by therapeutics employed and various routes of administration to maximize therapeutic efficacy while minimizing any potential adverse side effects. Pertinent medications in LTS management include corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, biologics, and immunosuppressive therapies (**Table 1**)[27-70].

Corticosteroids. Anti-inflammatory medications have long been part of treatment algorithms to minimize and improve healing in LTS, and corticosteroids have played an integral role. The earliest clinical reports regarding corticosteroid use in LTS were published in 1961[71]. These studies evaluated intravenous (IV) steroids in pediatric patients. Steroids have been used as a post-intubation treatment to control LTS, edema, relieve subglottic pressure, and also help decrease airway resistance[72]. Various studies have been conducted on the impact of steroids for LTS symptom management in clinical and *in vivo* assessments (**Table 1**). Steroid therapy (i.e., glucocorticoids) leads to a significant decrease in inflammation and chondrocytes proliferation as

well as a reduction of vascularization at the site of injury in rats' larynx and trachea[33].The underlying mechanism by which steroids prevent granulation tissue relies on two main phases: (1) The initial impact of steroids on TGF-β1 signaling by regulation of TGF-β1 binding to receptors on respiratory fibroblasts[73, 74]; and (2) the impact of the steroid's concentration and dosage to continually impede the activation of the TGFβ pathway[27, 75].

Non-steroidal anti-inflammatory drugs. NSAIDs are most often used mostly as analgesics and have shown more limited efficacy with regards to LTS treatment compared to corticosteroids. Intramuscular (IM) administration of diclofenac, an anti-inflammatory NSAID, was found to decrease inflammation, fibrosis, necrosis, and neo-chondrogenesis without affecting vascularization at the injury site in a preclinical rat model of tracheal wounds[33]. Employing tenoxicam[37] in the rat tracheal injury model by intraperitoneal injection was found to improve epithelial healing and reduce fibroblast proliferation. Combined with specific antigenic inhibitors such as Nintedanib[68] administered as adjuvants, NSAIDs may be a suitable option for post-operative analgesic purposes.

Antibiotics. The native airway microbiome is altered in the laryngotracheal complex at mucosal injury sites during prolonged intubation[76, 77]. As bacteria associated with LTS[15] can cause prolonged chronic mucosal inflammation[78] and granulation tissue formation[79], modification of the local microbiome may help mitigate development of LTS. Various aerobic pathogens, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus viridans*, *Haemophilus influenzae*, and *Neisseria*[79-81] have been associated with upper airway infections and with causing extensive tracheal granulation even outside the setting of an acute infection. Biofilm formation on endotracheal tubes, promotes bacteria survival and prolongs local inflammatory responses since pathogens within biofilms are resistance to antibiotic treatments[82]. Fungal infection and the presence of yeasts (i.e., *Candida*[83]) during prolonged intubation is another less common complication found most commonly in patients with prolonged inhaled steroid use or immune dysregulation[83]. Studies are limited regarding the clinical impact of fungal infection on progression or treatment of LTS[82]. Some antibiotics such as doxycycline have been employed in preclinical studies in rabbits to successfully modulate tracheal inflammation and reduce granulation tissue[29] since it is a tetracycline that inhibits both collagen synthesis and degradation[84]. Similarly, rapamycin, an immunosuppressive drug that has been studied to directly inhibit LTS by blocking fibroblast proliferation and metabolism[55], is also an antibiotic.

Biologics. Over the past two decades, several studies have investigated the specific pathways and pertinent gene regulation during scar tissue formation in LTS[10]. Since TGFβ1[13, 85] was identified as a key growth factor in fibro-inflammatory conditions, several studies have tested the effect of TGFβ1 inhibitors, primarily in preclinical animal studies. Exposure of the laryngotracheal wound site to TGFβ1 antibodies in rat models led to reduced fibronectin and type I collagen[32] production. A preclinical canine study confirmed that the TGFβ1 antibody decreased tracheal stenosis and increased the survival time compared to a control group[62]. Other biological agents targeting the TGFβ pathway focus on the downregulation of receptor-regulated effector proteins such as SMAD3 and SMAD2[86]. Small interfering RNA (siRNA) targeting *smad3* have been shown to abrogate fibroplasia *in vitro*[87] and in preclinical studies in rabbit models of vocal fold fibrosis[57]. Silencing IL-17, a cytokine responsible for chronic inflammation

is another potential route for LTS management. It has been investigated in terms of reducing fibrosis in the trachea, but additional studies and further evaluation are required for therapeutics targeting IL-17 independently in LTS management[15]. In addition, Prostaglandin E2 (PGE2) is an inflammatory mediator in the lower airway, and it has also shown anti-fibrotic properties in vocal fold fibroblasts[88, 89] with a ubiquitous role in both the early and late stages of wound healing[90]. While this finding demonstrates potential for stimulating epithelial migration and inhibiting a profibrotic response [90], preclinical and clinical evaluations are needed to understand the impact of PGE2 as a targeted therapeutic. LTS due to tracheal cartilage damage typically requires surgical resection and reconstruction. After surgical reconstruction, bFGF stimulation has shown promise in promoting tracheal cartilage growth[65]. In preclinical studies conducted in rabbits, either direct intratracheal injection of bFGF [45] or the release from the hydrogel-based scaffolds[65] resulted in improved cartilage growth and lumen enlargement.

Immunosuppressive agents to control LTS. Various immunosuppressive agents have been tested and approved by the Food and Drug Administration (FDA), mainly to prevent organ rejection, as chemotherapy medications, and to limit granulation tissue formation. There are a limited number of immunosuppressive agents that have been evaluated specifically for the control of LTS in clinical or preclinical studies. Among them, administration of tacrolimus has been reported to reduce stenosis. *In vivo* evaluation of the systemic administration of tacrolimus in rat models shows that the LTS could be controlled by inhibiting the activation of immune cells present in mucosa through the calcineurin/nuclear factor of activated Tcell/interleukin 2 pathway[52]. In a clinical study conducted on 19 patients with benign airway obstructions[61], the low dose systemic administration of tacrolimus had an inhibitory effect on tissue granulation, especially in patients who underwent airway stent insertion. This data suggests that further investigation of local release of drugs through stents or the use of other similar medications such as sirolimus on LTS management is warranted[61]. Rapamycin is another FDA-approved immunosuppressive agent with both antibiotic and anti-proliferative functions and is mainly prescribed as an anti-rejection agent[39]. *In vitro* studies on the impact of rapamycin have shown a significant decrease in cell proliferation of human LTS derived fibroblasts and associated collagen I expression [15, 55]. *In vivo* evaluation of rapamycin-elution from stents in LTS management in mice demonstrated a marked reduction in the thickness of the lamina propria and in the expression of TGF-β [91]. The impact of rapamycin on preventing or delaying LTS recurrence however remains an open question. Mitomycin C, a chemotherapeutic alkylating agent, has been administered topically to prevent LTS recurrence and granulation tissue formation[30, 56, 92]. Patients who underwent endoscopic laser surgeries showed a 93% improvement of airway resolution when they received local administration of Mitomycin C[59] .

Drug Delivery Approaches in LTS

The first tracheostomy was recorded in 2,000 BC[93]. Cuffed ETTs were first introduced in 1893[94], however the adverse effects of post-intubation and post-tracheostomy stenosis were not addressed by drug delivery systems until the 1960s[67]. A timeline of technological developments in addressing LTS are schematically represented in **Figure 2** [24, 35, 38, 42, 46, 47, 50, 51, 54, 63, 65, 95-102]**.** Multiple strategies for drug delivery have been developed since aerosolized dexamethasone was first administered to treat subglottic stenosis in 1992 (**Table 1**). These approaches are especially critical since the complex three-dimensional laryngeal anatomy, natural mucocilliary clearance mechanisms, and lack of easy access limits drug delivery and

therapeutic efficacy. Poor local bioavailability in the laryngotracheal complex make oral administration most often impractical, as patients are exposed to medication side effects, as seen with suppression of the hypothalamic-pituitary axis when using oral corticosteroids. Direct topical application is limited to short intra-operative applications as is the case with Mitomycin C, which limits it's role in post-op treatment to potentially prevent recurrence. The primary routes of drug administration are discussed below.

Intravenous and intramuscular injection. The first published study (in 1961) on LTS management used employed IV injection of steroids in pediatric patients with LTS symptoms and edema, and reported that respiratory symptoms cleared after 3 hours of a single dose of diphenhydramine and dexamethasone [71]. Current surgical interventions are usually accompanied by various doses of IV steroid treatment in LTS patients[67]. In a recent study, administration of steroids via IV injection to LTS patients after ten days of intubation (due to SARS-CoV-2 infection) suppressed inflammation and resolved associated LTS symptoms without requiring further intervention[103]. Steroid IV injections have also been effective as an adjunct to budesonide nebulizers, anti-reflux therapy, and humidified oxygen to control LTS symptoms in pediatric patients[104]. Highly water-soluble compounds diffuse rapidly into circulation and can be delivered intramuscularly. Dexamethasone delivered pre-injury in a rabbit model by IM administration was effective in reducing airway stenosis[69], which shows that single-dose systemic dexamethasone can be considered to stave off iatrogenic stenosis from ETT placement and removal. While IV and IM have been the popular choice for corticosteroid delivery as an adjunct to airway management interventions, dosing by this route is usually limited to the initial 24 hours, and systemic adverse side effects on patients limit long-term application[105].

Aerosol delivery. Aerosol delivery has been widely used to treat airway disorders, especially for delivery of anti-inflammatory drugs. However, in most cases the delivery target is pulmonary rather than upper airway tissues. The delivery of corticosteroid and NSAIDs[106] using Pressurized Metered Dose Inhalers (pMDI)s or nebulizers[106]proved beneficial for pediatric patients with prolonged intubation history. Nasal sprays remain an administration platform of choice for pediatric patients even for delivery specifically to the upper airway[107]. Aerosolized budesonide combined with topical Mitomycin C provided after dilatation in patients with LTS grades I to III resulted in reduced recurrence of stenosis[56]. Dexamethasone has also been administered using aerosol delivery. In ferret models[46], dexamethasone was aerosolized and administered post-injury to prevent stenosis. Examinations revealed that aerosolized dexamethasone preserved the integrity of subglottic mucosa and reduced risk of laryngeal obstruction[46]. Aerosolized delivery has also been investigated in preclinical rabbit models of tracheal stenosis where nintedanib and budesonide were successfully delivered to the trachea by inhalation as aerosols[68]. However, concerns remain regarding systemic side effects and possible unintended deposition of the particles into the lungs. Moreover, aerosol inhalation of budesonide led to relief during bronchoscopy, but reported to not eliminate restenosis[49].

Site-specific injections. Intralesional steroid injections have been successfully used clinically for conservative management of laryngotracheal stenosis and are especially effective if the lesion is at an early stage[108]. Serial awake intralesional steroid injections were extensively investigated by Franco et al. [109] using both trans-cricothyroid as well as trans-nasal approaches for 4-6 injections separated by 3-5 weeks and shown to be effective at airway patency

improvement. Intralesional injections are often used as an adjunct to surgical interventions, used to modulate the scar tissue post-surgery to prevent recurrence as well as used as an early intervention to prevent stenosis from deteriorating. In a retrospective study of idiopathic subglottic stenosis, a combination of laser resection with intralesional corticosteroid injection and topical mitomycin-C was effective but stenosis recurred within 5 years[110]. Betamethasone, dexamethasone, and triamcinolone acetonide are commonly injected corticosteroids (**Table 1**). Intralesional injections of encapsulated drugs (5-fluorouracil) at site in a preclinical rabbit model showed improved uptake in underlying tissue compared to free drugs indicating that multi-level targeting is possible using site-specific injection[38]. Office-based site-specific injections are generally repeated every 3 to 4 weeks, a delivery regimen that proved effective to shift a profibrotic site to an anti-fibrotic scar milieu[64]. While serial office-based steroid injections showed promise in controlling airway stenosis, there are certain limitations, including (1) lack of defined safety protocols; (2) practical restrictions to patients with subglottic stenosis; (3) high frequency of required treatments and monitoring; (4) required local or general anesthesia for each treatment; (5) effectiveness only in patients with 50% or less stenosis[40].

Topical and Oral Delivery. Topical delivery of drugs to upper airway stenosis sites is achieved by using pledgets and mitomycin-C is often the drug of choice for such administration. Soaked mitomycin-C pledgets directly applied to the mucosa paired with dexamethasone treatment [111] or laser endoscopic management[59] in adults and paired with balloon dilation in pediatric patients[56] have been effective at resolving LTS clinically. However, there is potentially a narrow therapeutic window since Hueman and Simpson [112]reported a higher incidence of complications with higher concentrations of mitomycin-C (10 mg/ml vs 0.4 mg/ml) as an adjuvant in laser laryngoscopic treatment and dilation of the upper airway. Complications including sever fibrous tissue proliferation were also observed preclinically at high doses in a rabbit model suggesting mitomycin-C dosage should be carefully assessed[113]. Oral prednisolone treatment in a randomized clinical trial showed some impact on the length of tracheal resection necessary compared to placebo, indicating that oral corticosteroid therapy has value as an adjunct in the management of post-intubation stenosis[60]. Oral colchicine therapy has been reported in combination with tracheal stenting to prevent tracheal collapse in a canine case study, but a narrow therapeutic index in human and veterinary care limit use of the drug since higher dosages are associated with systemic shock[114]. In a preclinical study in rabbits, a combination of erythromycin (oral delivery) with aerosolized budesonide resulted in a reduction in the thickness of the epithelium and lamina propria after a tracheal stenosis model was established[36]. Oral administration is affected by the same systemic off-target effect limitations that are considerations in IV an IM administration.

Drug Eluting Endotracheal tubes. Drug delivery using endotracheal tubes primarily targets LTS prevention by immediately treating local mucosal injury and reducing incidence of fibroplasia and granulation tissue formation. It should be noted that this drug delivery is not through the lumen of the ETT, but from or through the curved surface on the outside of the ETT that is in mucosal contact. Corticosteroid delivery through the ETT lumen results in distal delivery (rather than to the mucosa damaged by intubation) and carries with it the associated risks of any systemic corticosteroid therapy[115], as discussed in the cases of IV and IM delivery. Endotracheal tubes provide a unique opportunity for drug delivery because they are in prolonged contact with the larynx in the intubated patient as the ETT curves from the oropharynx, coming into contact

with the posterior glottis and vocal folds as it passes through to the trachea. Local drug delivery for iatrogenic laryngotracheal disorders uses polymeric or composite materials, with designed material properties mainly focused on modifying the ETT to introduce smart drug delivery systems (**Table 1**). A wide variety of biocompatible materials have been developed over the last two decades for various administration applications, making effective and targeted drug delivery possible. Antibacterial coating of endotracheal tubes with silver or other molecules[116]demonstrated the promise of this approach in preventing biofilm formation. ETT surface modification with PLGA and incorporating Lasioglossin-III for drug release, was studied *in vitro* and shown to be safe for fibroblasts and epithelial cells while exerting an antibacterial effect on *Staphylococcus epidermidis* [117]. In a different *in vitro* study, Poly(N-isopropylacrylamide (P(NIPAA)) - polycaprolactone (PCL) coatings were developed to achieve thermosensitive release of metronidazole (an antibiotic) at physiologic temperatures[42]. The objective of these studies is primarily to incorporate antimicrobials to prevent biofilm colonization of the ETT surface while not being cytotoxic to the cells of the upper airway – namely the fibroblasts and epithelial cells. Hexetidine-impregnated polyvinyl chloride (PVC) coatings [118] and Gentian Violet and chlorhexidine[119] dip coatings of ETTs are further examples of this approach.

The ETT and ETT cuff have previously been used as drug delivery platforms. While not in the context of LTS, anesthetics such as lidocaine have previously been released from the ETT cuff inflation solution in clinical studies by diffusion; to ease pain and increase tolerance during extubation[96, 120]. Similarly, electrospinning, a biomaterials-related technique provides a versatile platform to fabricate polymer-based drug-incorporated systems. Deposition of electrospun poly (lactic-co-glycolic acid) (PLGA) fibers around ETTs and successful release of mometasone furoate from these PLGA fibers over 14 days has been demonstrated [95]. *In vivo* evaluation of this platform in a rat model indicated a decrease of laryngeal mucosal thickness and submucosal gland edema upon drug administration[95]. A follow-up *in vivo* study in rats using the same platform, provided evidence of reduced airway morbidity after prolonged intubation [121]. PCL coatings on ETT surfaces that provided sustained delivery of phlorotannin; an anti-inflammatory functional polyphenol extracted from brown algae [47], showed decreased collagen deposition and granulation in a rabbit model[47]. These studies indicated the importance of local drug delivery from ETTs during intubation and prevention of LTS at the early stage of fibrosis and granulation formation without systemic side effects.

PLGA, PCL and the previously mentioned polymers form a relatively stiff coating on the ETT surface and care should be taken to not exacerbate injury to the mucosa when using these coated tubes. In this regard, hydrogels, a class of hydrophilic polymers, have excellent capacity for drug delivery by diffusion, while hydrogel modification of ETT surfaces can result in much softer mechanical properties and potentially provide a self-lubricating environment between ETT and the inner mucosal lining. While applications of hydrogels to leverage self-lubricating properties have been previously indicated[122], studies pertaining to their specific application in LTS management are needed.

Implant-based drug delivery. Dilatation and laser therapy are endoscopic surgery techniques used to manage LTS without open surgery. However, patients are frequently subjected to repeated treatments due to LTS recurrence without resolution of the underlying condition causing fibroplasia. Many of these therapeutic administrations can be performed in the office setting without sedation. Tracheal stents, the first implant-based systems developed in 1990[123]

and used for LTS management, have been comprehensively reviewed by us previously[124]. Stent designs, later modified to incorporate different eluting drugs[100], are one of the most widely used tracheobronchial prostheses and yield promising therapy. In general, metals such as nitinol, steel, and magnesium alloys are used for airway stents, but lack the capacity for drug loading. To overcome this limitation, polymeric stents and coated stents have been developed [63, 100] to incorporate drugs within the polymeric coating phase for subsequent controlled delivery. The biocompatible polymers used in these stents are generally biodegradable, such as polycaprolactone[63, 125, 126], poly-L-lactic acid (PLLA)[63, 125], poly (lactic-co-glycolic acid) (PLGA)[63, 127], and polypropylene[128, 129]. These polymers possess higher mechanical properties needed to maintain the stent shape during stenting. These stents were loaded with various drugs such as dexamethasone[130, 131], paclitaxel[132], rapamycin[34], methylprednisolone succinate[63], and mitomycin C[125]. While airway stents are a promising long-term alternative to treat LTS, serious complications detract from stenting, including stent migration, tissue granulation, infection, and stent fragmentation, which remain open challenges in implant-based drug delivery towards LTS management. A stent design using a combination of knitted PLGA mesh, collagen type I and a secondary gelatin hydrogel layer was used to provide coverage on injured trachea sites and used to deliver bFGF to initiate tracheal defect repair[65]. The slow release of bFGF corresponding to the rate of gelatin degradation was reported to reduce the early inflammatory response and no record of tracheal collapse was observed in a rabbit model[65]. While stents remain the major class of tracheobronchial prostheses, other unique designs with different drug-delivery strategies have also been developed in the last decade. They are much less commonly employed in the treatment of LTS.

In our recent work on bio-inspired adhesive patches, we developed hydrogel based patches loaded with dexamethasone to provide tunable drug-delivery to administer dexamethasone in burst bolus and/or sustained release[51]. Adhesive patches were developed by incorporating hydrogel-based pillars on top of a PCL electrospun membrane, with the pillars promoting adhesion to the inner lining of the trachea. Dexamethasone could be incorporated and released from both the hydrogel pillars (burst release) and the PCL membrane (sustained release)[51]. *In vivo* studies to test efficacy of this dual-phase drug delivery on LTS therapy and the potential to promote epithelial regeneration are yet to be conducted.

Tracheal prostheses fail due to the high risk of restenosis after LTS treatment. To address this, a 3D printing technique was used to fabricate tranilast-loaded tubular scaffolds to suppress stenosis through sustained local delivery of tranilast[28]. Tranilast is an inhibitory agent of TGF-β that suppresses synthesis of collagen types I and III. In this study, the prosthesis was implanted into the rabbits' trachea for circumferential tracheal reconstruction and reduction in restenosis and sustained anti-inflammatory tissue responses were observed over 30 days [28]. Another study[48] combined electrospinning with 3D printing to fabricate 3D scaffolds made of PCL loaded with dexamethasone to reduce stenosis in a rabbit model[48]. At four weeks after implantation, enhanced anti-inflammatory response and indications of mucosal regeneration were observed indicating potential applications for use in tracheal transplantation therapy and LTS management [48].

Preclinical Screening Models and Drug Delivery Systems for LTS

Drug delivery systems for LTS management have been extensively tested *in vitro*, *ex vivo*, and *in vivo* where the animal models are generally chosen and studies designed based on time limits, costs, and the scalability of the designed drug delivery system. Among these animal models,

rodents have been widely used for administration by injection [33, 37, 66], stent-based systems[95, 121], and oral administration[84] techniques towards LTS management. While the small size of rodents limits flexibility regarding administration technique, the benefit is the relatively shorter duration of *in vivo* testing. Rabbits are the model of choice for studies using 3D- printed tubes[28], stents[29], injection[30, 41, 57], ETTs[47], scaffolds-based stents[125, 130], and aerosol inhalation[68], typically lasting for up to 12 weeks duration. While rabbits have been selected for testing biological medications[45, 65] in LTS management, monkeys[72], dogs[62, 131, 132], and sheep[129] are preferred for testing biologic efficacy since the immune/inflammatory responses of larger animals is more similar to clinical outcomes. Among these large animal models, pigs have the most similar upper respiratory anatomy to humans. This model has been extensively used to investigate vocal fold damage caused by intubation[133] or laryngotracheal burn models developed by the authors[134]. In addition, we investigated the mechanical properties changes of the laryngeal tissue in healthy and fibrotic conditions to distinguish mechanical markers of physiology versus pathological dysfunction[135, 136]. However, to date, the data regarding the application of large animal models in LTS management remains relatively limited owing to high costs and effort to care for them. A summary of the drugs, administration strategies, and duration of treatments on different animal models for LTS treatment are detailed in **Table 2** [28-30, 32-37, 41, 44, 45, 47, 57, 62, 63, 65, 66, 68, 72, 84, 121, 125, 129-132, 137, 138].

Table 1. Summary of common drugs and their physiological impacts, advantages, administration systems, and disadvantages in LTS management.

Effect	Drug	Mechanism	Administration	Stage	Study Design/Dosage	Observations and Considerations	Ref
Anti-inflammatory	Prednisolone	↓ migration of polymorphonuclear leukocytes	Oral Pill	Clinical	15 mg/day (up to 22 days)	Decreases edema associated with injury	[60]
	Dexamethasone	↓ fibrous tissue proliferation	IV Injection	Pediatric	0.5 mg/kg.day then 0.3 mg/kg.day (2 doses daily; 3 days each)	· ↓ Length of resection · Anti-inflammatory but may not be effective in case of fibrosis in the lung	[31]
			IV Injection	*In vivo*	Injection (1mg/kg) 1 hour pre-extubation and 6 hours post-extubation	No effect on laryngeal inflammation or tissue necrosis	[44]
			Intramuscular Injection	*In vivo*	Injection 2 mg/kg 15 minutes prior to operation	Demonstrable reduction in airway stenosis	[69]
			Aerosols	*In vivo*	Aerosolized 8 mg/kg drug at 2, 4, and 6 hrs post-injury	· Subglottic airway preserved · Reduction in post-injury edema	[46]
			Implant-based drug delivery	Design Development	Electrospun-flocked patch + drug Upto 1.6 mg/hr.cm^2 for 2 hours & upto 0.5 mg/day.cm^2 for 28 days	Sufficient adhesion to adhere to mucosa and controlled release of the drug *in situ*	[51]
			Implant-based drug delivery	*In vitro* and *In vivo*	Maximum 1mg/ml of drug loaded into 3D tubular scaffold of surface-modified PCL electrospun fibers	· Higher cell adhesion and anti-inflammatory response · Reduction of restenosis at tracheal anastomosis	[48]
	Triamcinolone Acetonide	Suppression of fibroblast proliferation	Implant-based drug delivery	Design Development	3D printed steroid-eluting subglottic stenosis stent containing 400 mg of the drug	· AutoCAD to personalize stent · No *in vitro, in vivo* testing	[50]
			Injection into paratracheal/laryngeal soft tissues	*In vivo*	Injection of 5 mg	Reduction in fibrosis when combined with 5-fluorouracil	[30]
			Local injection into the injury (one-time)	*In vivo*	10 mg suspended in hyaluronic acid gel	Stenosis reduction (after squamous metaplasia surgery) combined with 5-fluorouracil	[41]
	Triamcinolone acetate and dexamethasone	↓ fibrous tissue proliferation	Intralesional injection	Clinical	Transcricothyroid: 2ml with Triamcinolone acetate (40 mg/mL) and dexamethasone (4mg/ml)	· Shorter procedure length · Limited by the presence of cricothyroid space	[64]
	Betamethasone	↓ TGF-β1 ↓ collagen deposition ↓granulation tissue	Local injection (one-time)	Pediatric	2 ml (larynx)	Limited evidence for treating severe subglottic lesions	[43]
			Local injection (one-time)	Clinical	0.2–0.4 ml (local injection)	↓↓TGF-β1 expression	[27]

			Office-based steroid injection	Clinical	Transcervical injection 6 mg/ml	Decreased average stenosis	[40]
	Budesonide	↓ inflammation & fibrosis, Prevent restenosis	ET tube-based delivery	Device Development	Aerosol delivery of budesonide in nanoparticle form through ETTs	Higher emitted dose compared to stock budesonide	[58]
			Aerosols	Clinical	Aerosol inhaler (200 μg, 2 times daily) for 2 weeks	↓ stenosis recurrence	[56]
			Aerosols	Clinical	Budesonide inhalation after small-diameter tube-assisted bronchoscopic balloon dilatation	↓ stenosis recurrence	[49]
			Aerosols	*In vivo*	Inhalation 1000 μg/day drug suspension 7 days pre-surgery, and 10 days post-surgery	Reduction of targeted fibrotic factors when combined with erythromycin	[36]
	Diclofenac	Blocks chemotactic molecule synthesis	Intramuscular Injection	*In vivo*	10 mg/kg/day Intramuscular injection for 7 days	↓ Inflammation and fibroblast proliferation	[33]
	Tenoxicam	↑ Epithelial regeneration, ↓ Fibroblast proliferation	Intraperitoneal Injection	*In vivo*	0.5 mg/kg/day Intraperitoneal injection for 10 days	· Decreased inflammatory cell infiltration and increased angiogenesis in trachea · Improves epithelial vs. fibroblast proliferation	[37]
	Pirfenidone	↓ TGFβ-1, TNFα, and IL-1β production	Intraperitoneal Injection	*In vivo*	Injection of 15 mg/kg/day, 1 mL pirfenidone solution for 10 days	· Reduction in TGFβ-1, TNFα, and IL-1β expression · ↓↓ Fibrosis & inflammation. · Preserves lumen diameter	[66]
	Methylprednisolone acetate	↓ fibrous tissue proliferation and inflammation	Office-based steroid injection	Clinical	1ml (40 mg/mL) of drug by intrafold injection into superficial lamina propria	· Vocal fold scars improved after injection with improved voice grade, amplitude, mucosal wave · Two of 18 patients could not tolerate injection technique	[54]
	Methylprednisolone Succinate	Prevents granulation tissue development after tracheal surgery	Implant-based drug delivery	*In vivo*	Drug-eluting PLA, PLGA, and PCL stents with drug (20 mg/mL) coating for release over 10 days	· Suppression of granulation tissue with PLA, PLGA · PCL coated stents showed aggravated inflammation.	[63]
	Nintedanib	↑ HDAC2 expression, ↓ Il-8 and VEGF expression	Oral- Gavage	*In vivo*	30, 60, or 100 mg/kg daily by gavage	· Very low drug solubility limits effectiveness · Anti-inflammatory and anti-fibrotic activity	[70]
			Aerosols	*In vivo*	10 mg/kg aerosolized drug twice daily for 10 days	· Reduces tracheal stenosis and inflammation	[68]

Immuno-suppressive	Paclitaxel	↓ Cell growth/anti-proliferative	Implant-based drug delivery	*In vitro*	Controlled drug release from nanoparticles for stent coating	· Paclitaxel had inhibitory effect on cell viability	[53]
	5-fluorouracil	↓ fibrous tissue proliferation	Office-based steroid injection	*In vivo*	5-fluorouracil (free or encapsulated)	· ↑ Scar permeation and inhibits scar formation · Disrupts DNA, RNA synthesis	[38, 41]
	Rapamycin	Binds FKBP12 to inhibit mTor, suppresses fibroblast proliferation and collagen synthesis	Implant-based drug delivery	*In vivo*	70-75 µg drug/day for 14 days by drug-eluting PLA-PCL stent	· 70:30 composition of PLA: PCL identified as optimal	[34]
			Direct exposure	*In vitro*	1 ng/mL	· Possible systemic effects (i.e., hyperlipidemia, anemia, thrombocytopenia)	[39, 55]
	Tacrolimus	Inhibits of calcineurin/ nuclear factor of the T-cell/ IL-2 pathway	Intramuscular Injection	*In vivo*	Intramuscular injection of 0.2- 1.0 mg/kg for 5 days	· Mucosal layer modulation · Prevent LTS in acute injury	[52]
			Implant-based drug delivery	Clinical	Tacrolimus (titrated to 8-12 ng/mL of whole blood)	· Reduced granulation tissue · Inhibits immune cell activation in airway mucosa · Dose-dependent toxicity on epithelial cell proliferation	[61]
	Mitomycin-C	↓ fibroblast proliferation	Topical Application	*In vivo*	Topical application of 0.14 mg Mitomycin	Significant reduction in the severity of LTS	[35]
			Topical Application	*In vivo*	0.4 mg/mL (10-mm sponge) for 4 minutes	· Modulates wound healing to ↓ scar formation · Causes a lack of complete mucosal regeneration	[30]
			Topical Application	Clinical	0.4 mg/mL applied topically by cottonoid sponge for 4 minutes	Minimize scar formation	[59]
			Topical Application	Clinical	Application before tracheostomy, stent insertion, and dilation	Risk of recurrence	[67]
Biologics	siRNA targeting *smad3*	Knock down *smad3* transcription and translation	Local Injection	*In vivo*	20 pmol by injection	· ↓TGF-β expression · ↓Collagen IA1 expression · Poor transfection efficacy	[57]
	TGF-β antibody	↓ fibronectin ↓ type I procollagen	IV Injection	*In vivo*	5 mg/kg on Day 0 and Day 5	· ↓ tracheal stenosis · ↑ survival time	[62]
			Osmotic pump infusion	*In vivo*	1.25 ng/µl	↓ Extracellular matrix protein expression	[32]
	bFGF	Promotes growth of native tracheal cartilage	Local Injection	*In vivo*	One time injection of 100- 200 µg into the posterior wall of the cervical trachea	· ↑ tracheal cartilage growth · Sustained release for uniform cartilage growth	[45]

			Implant-based drug delivery	*In vivo*	100µg bFGF impregnated gelatin hydrogel in PLGA–collagen hybrid scaffold reinforced with a PCL stent	· Tracheal cartilage growth, enlarged tracheal lumen · Effects muted at low dosage · Possible fragmentation of scaffolds is a concern	[65]
Others	Metronidazole	Antibacterial effect	ET tube-based delivery	Device Development	1% w/w drug:PCL from p(NIPAA-co-HEMA) hydrogels	"smart" thermosensitive drug release	[42]
	Phlorotannin	↓ fibrogenesis & tracheal submucosa thickening	ET tube-based delivery	*In vitro* and *In vivo*	Polycaprolactone/Phlorotannin (2g) endotracheal tube	Capable of steady release for up to 7 days	[47]
	Tranilast	↑ anti-inflammatory response	Implant-based drug delivery	*In vivo*	20mg from 3D printed tubular scaffold and surgical suture	Reduction of restenosis	[28]
	Doxycycline	↓ inflammatory cells and reduced fibrosis	Implant-based drug delivery	*In vivo*	Nitinol stent coated with doxycycline (30mg)	*smad3* expression changed	[29]

Acronyms/abbreviations: TGF-β: Transforming Growth Factor-beta, bFGF: basic Fibroblast Growth Factor, siRNA: Small interfering RNA, FKBP12: FK506-binding protein 12, IL-2: Interleukin-2, LTS: Laryngotracheal Stenosis, IV: Intravenous Injection, HDAC2: Histone Deacetylase 2, VEGF: Vascular Endothelial Growth Factor, TNFα: Tumor Necrosis Factor-alpha, IL-1β: Interleukin 1 beta. TNF: Tissue necrosis factor, IL: Interleukin, HDAC2: Histone deacetylase 2, pMDI: pressurized metered-dose inhaler, VEGF: vascular endothelial growth factor, DNA: dioxy ribonucleic acid, RNA: ribonuceleic acid, ETTs: Endotracheal tubes, p(NIPAA-co-HEMA): Poly(N-isopropylacrylamide-co-hydroxyethyl methacrylate), PCL: polycaprolactone, PLA: Poly(lactic acid), PLGA: poly(lactic-co-glycolic acid).

Table 2. Preclinical animal models employed to determine the safety and efficacy of therapeutics for LTS treatment.

Model	Injection		Stents		Endotracheal Tubes		Inhalation		Others	
	Drug	**Dosage**	**Drug**	**Dosage**	**Drug**	**Dosage**	**Drug**	**Dosage**	**Drug**	**Dosage**
Murine	Diclofenac Dexamethasone [33]	10 mg/kg/day 2x 0.1 mg/kg/day (for 1 week)	Rapamycin[34]	70-75 µg (> 2 weeks)	Mometasone furoate[121]	100% of loaded drug (for 14 days)	-	-	Anti TGFβ1 via osmotic pump infusion[32]	10 ng/hour (24 hours)
	Tenoxicam[37]	0.5 mg/kg/day								
	Pirfenidone[66]	15 mg/kg/day (for 10 days)							Doxycycline Oral admin [84]	40 mg/kg (≤5 weeks)
Leporine	siRNA targeting *smad3*[57]	20 µL at 20 pmol siRNA single dose	Mitomycin C[125]	0.1 mg (over 12 weeks)	Phlorotannin [47]	3.64 mg/ml (over 7 days)	Nintedanib, Budesonide[68]	10 mg/kg 0.05 mg/kg	Topical mitomycin-C 5-fluorouracil /triamcinolone [30]	0.4 mg/mL (on the wound for 5 min) 5 mg in 0.2 mL sodium hyaluronate (injected)
	bFGF[45]	200 µg bFGF single dose	Methylprednisolone succinate[63]	1 µL at 20 mg/mL						
	5-fluorouracil + triamcinolone [41]	2.5 mg co-drug in 0.2 mL hyaluronic acid gel	Dexamethasone [130]	0.02–0.05 mg/day for 30 days						
	Erythromycin + budesonide [36]	1000 µg/day (7 days pre- and 10 days post- surgery)	bFGF[65]	100 µg total (over 4 weeks)					Tranilast in 3D printed PCL tubes [28]	20 mg (over 14 days)
	Dexamethasone [44]	1 mg/kg (Pre-extubation, 6 hr post-extubation)	Doxycycline[29]	30 mg on nitinol stents					Heparin by autograft transplant tissue soaking [138]	5000 U/ml (1 time)
			Cisplatin[139]	100% of drug (over 32 days)						
Canine	anti-TGFβ1[62]	5 mg/kg (on day 0, day 5) + 50 µg at site (on day 0)	Dexamethasone [131]	36.7 mg total (≤4 weeks)	-	-	Beclomethasone [137]	450 mg/ day (15 days)	Mitomycin: Saturated applicators[35]	0.14 mg Mitomycin at 0.2 mg/mL (on day 0, day 2)
			Paclitaxel[132]	0.0225 g total (5 months)						
Ovine	Carpofen and buprenorphine [129]	carprofen 4 mg/kg IV single dose	-	-	-	-	-	-	-	-
Primate	Dexamethasone [72]	4 mg/kg (for 1 hour post-extubation)								

Blue indicates anti-inflammatory drugs, yellow indicates immunosuppressive drugs, green indicates antibiotics and red indicates biologics.
Acronyms/abbreviations: 2x: two times, IV: intravenous, PCL: Polycaprolactone. TGFβ1: Transforming Growth Factor-beta, siRNA: Small interfering RNA, bFGF: basic Fibroblast Growth Factor.

Limitations of Current Clinical Drug Delivery Approaches for LTS

Currently, clinical treatment options for the prevention of posterior glottic, subglottic, and of tracheal stenosis remain limited and management to stave off iatrogenic stenosis includes minimizing the length of intubation and utilizing the smallest possible ETT. Often, a patient's medical condition dictates ETT size and the duration of intubation. Glucocorticoids, such as dexamethasone, reduce airway inflammation and are the most commonly used drug to treat airway stenosis, however their intralesional or topical applications are limited by difficulty in accessing the site during the acute period where life-threatening injuries are generally the focus of clinical care. In addition, the use of prolonged steroid treatment has adverse effects (either off-target or systemic) while achieving limited local pharmacological dosing to the region of interest.[40, 60, 137, 140-142] Furthermore, many other topically-used drugs (such as, mitomycin C) are either not readily available or impractical for systemic intravenous use or have a narrow therapeutic window. While limitations in current technology pertaining to ETTs restricts treatments of ventilator-dependent patients, ETTs themselves are a nidus for biofilm formation and propagation of infection[117]. In addition, while many studies have investigated stent-based drug delivery systems, clinical complications with deployment of airway stents remain unresolved. For this reason, effective local and targeted drug delivery systems for effective LTS management are needed. Different classes of "smart" polymers with local and targeting drug release capabilities and fabrication methods have been developed and tested for various applications in the last two decades. However, LTS management still relies primarily on conventional clinical techniques (injections and topical application), and the demands for innovative efficacious drug administration remain unmet.

Questions for Future Research

Although numerous studies have targeted the lower respiratory tract/lungs for fibrosis treatment, targeted topical drug delivery techniques for upper respiratory tract disorders such as laryngotracheal stenosis are yet to be fully explored. Although steroids and antibiotics have become routine in LTS treatment, they are primarily symptomatic suppressors. In addition, while biological modulators hold promise to target underlying pathophysiology and could lead to a paradigm shift in LTS management, further clinical data are required. The nature of LTS will require "smart" and local drug delivery to target scar and granulation tissue in a targeted fashion without systematic effect, and biomaterials science and novel drug delivery systems with smart delivery could offer clinical alternatives for safe and effective targeted drug delivery to treat LTS in the future. Similarly, redesigning endotracheal tubes or modifications to reduce mucosal damage could also further reduce incidence of LTS.

Conclusion

Laryngotracheal stenosis is a relatively rare but devastating condition with very limited treatment options. This life-threatening issue, as a result of prolonged intubation or tracheostomy, consists of scar tissue growth in the subglottic and tracheal areas which results in narrowing the airway due to the progressive fibrosis. Since the laryngotracheal space is relatively difficult to directly access, drug delivery approaches targeting laryngotracheal stenosis need to ensure topical and concerted action preventing inflammation/fibrosis in a sustained manner. Understanding the considerations of mechanism of action, route of administration, delivery technologies, and biomaterials-based drug delivery approaches in pre-clinical testing allows for clinicians to prepare for novel therapeutic interventions to alleviate stenosis and restore the airway.

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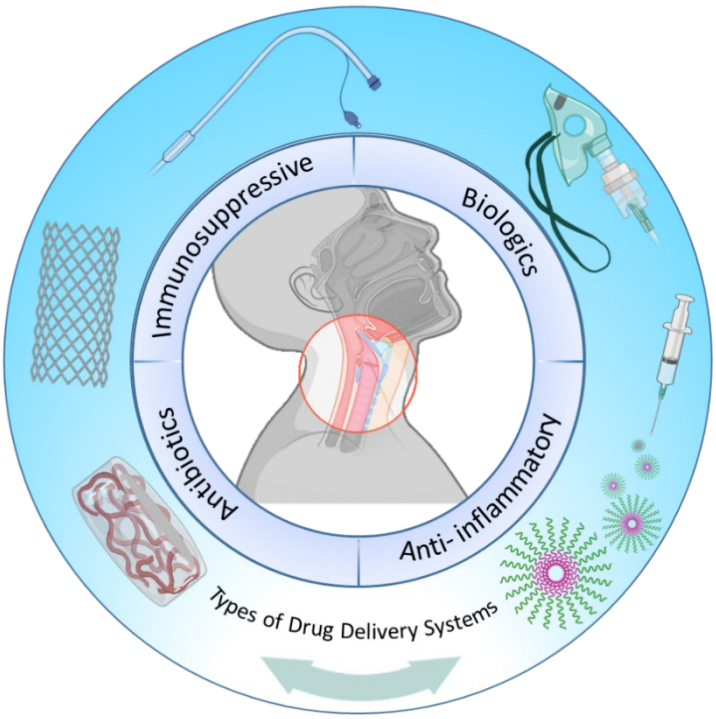

Suplementary Graphical Abstract

Figure Legends:

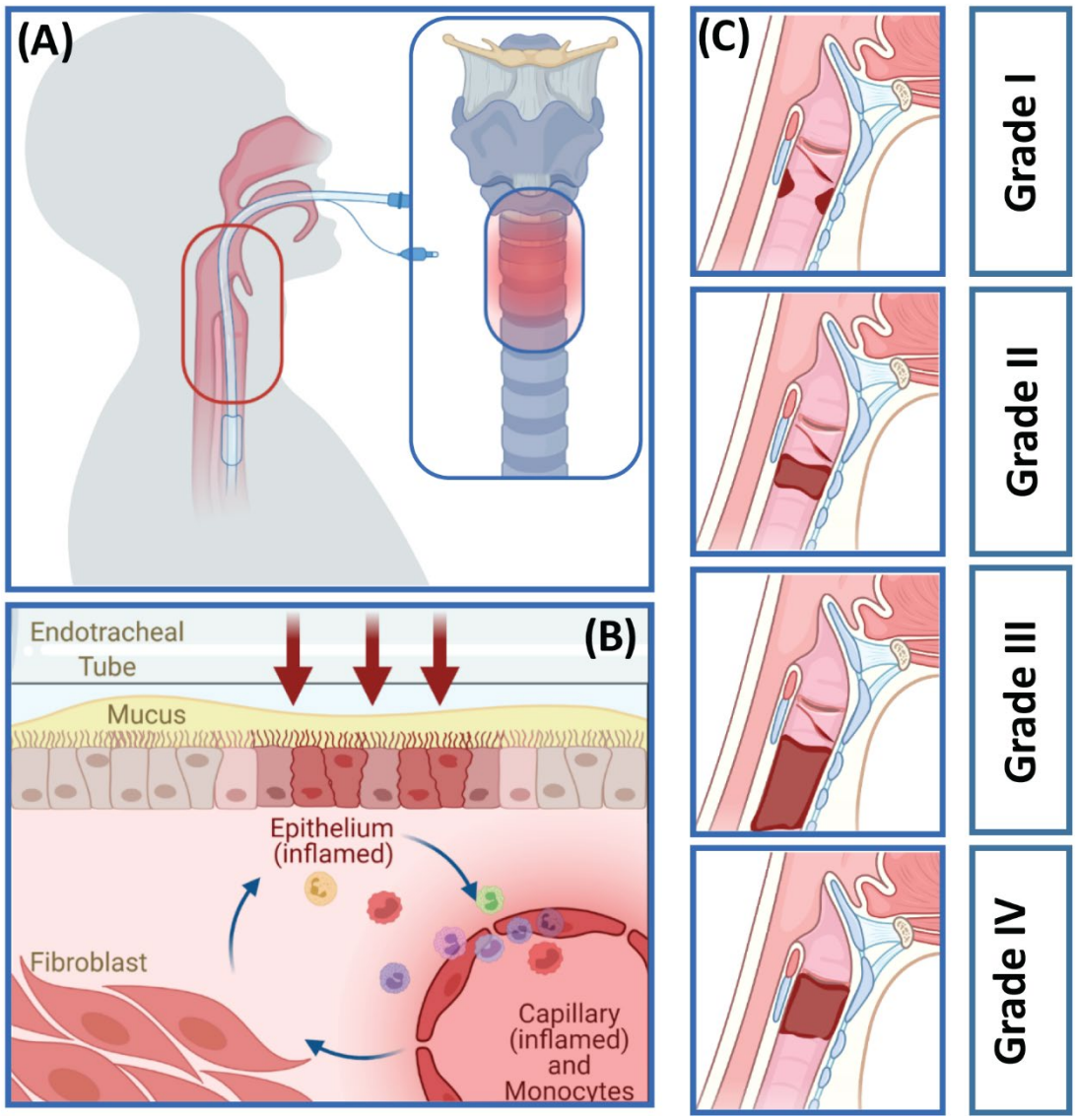

Figure 1. Schematic illustration summarizing possible iatrogenic LTS sites, pathophysiological pathways, and various LTS grades. (A) Subglottic and tracheal areas are in contact with the intubated endotracheal tube (ETT), which in prolonged intubation cases can cause scar tissue formation after the extubation. Furthermore, the curvature of the ETT through the larynx can put pressure on the vocal folds and posterior glottis creating addional sites of potential stenosis. (B) The sequence of pathophysiological sequences of the damage to the inner lining of the upper airway. Friction and pressure caused by ETTs damage and inflame the epithelial layer, which activates immune cells and fibroblasts' response to the inflammation in a positive auto-feedback loop, particularly if this epithelium was damaged or disrupted during intubation. (C) McCaffrey classification of LTS and laryngotracheal obstruction into four grades.

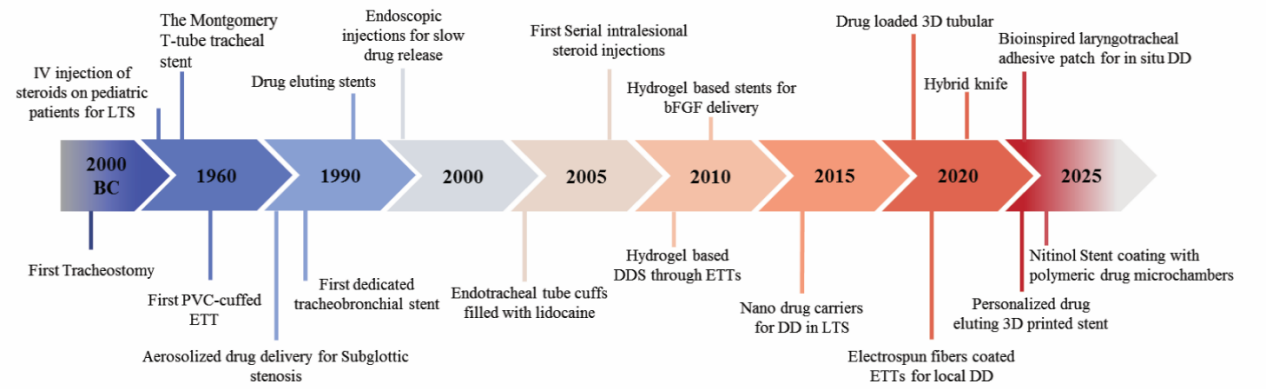

Figure 2. Timeline for strategies and drug delivery administration modalities used for LTS management since the 1960s [24, 35, 38, 42, 46, 54, 63, 65, 95-99, 101, 143-147]. LTS: Laryngotracheal Stenosis; ETT: Endotracheal Tube; DD: Drug Delivery; IV: Intravenous; 3D: three dimensional; bFGF: basic Fibroblast Growth Factor.