IJHSR
ijhighschoolresearch.org
■ REVIEW ARTICLE

A Comprehensive Review of The Impact on COVID-19 On Subglottic Stenosis

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ABSTRACT: SARS-CoV-2 is a new, widespread virus pandemic that started in late 2019. It targets the respiratory system, especially the lungs and airways, through the spread of infected water droplets being inhaled through person-to-person transmission. Current treatments include oral antiviral pills like Paxlovid and mRNA vaccines, but these treatments have limitations in not reducing the occurrence of a common side effect of COVID-19. In this paper, we study the correlation of how SARS-CoV-2 (COVID-19) in intubated patients on ventilators can develop subglottic stenosis (SGS) during such treatments. When SARS-CoV-2 patients are treated with these devices, their tubes can injure and possibly scar the airway epithelium, resulting in excessive scar tissue growth that blocks the airway, which is SGS. SGS arises when an injury in the airway stimulates rapid scar tissue growth to the point where the airway becomes too narrow and obstructed for breathing. It can also lead to the entire airway collapsing in severe cases. Even then, many current treatments for SGS, such as laryngotracheal reconstruction (LTR) and partial cricotracheal resection (CTR) surgeries, make the condition of the patients worse, especially with long-COVID patients with comorbidities potentially having a collapsed trachea. Thus, it is essential to find novel treatments to lower the risk of SGS in patients with such severe cases of COVID-19. Therefore, in this work, we discuss novel therapies to treat SGS cases that have been occurring from incidences of COVID-19 as a way to improve patient outcomes and save lives.

KEYWORDS: Biomedical engineering; SARS-CoV-2 (COVID-19); Subglottic stenosis; Endotracheal tubes; Antimicrobial peptides.

■ Introduction

1.1. Context on Subglottic and its Connection to SARS-CoV-2:

Subglottic stenosis (SGS) is a disease of the upper airway that affects around 2% of hospitalized patients on ventilators that have been bombarded with SARS-CoV-2 (COVID-19) viral infection.[1] SGS is defined as a disease where, due to injury from an endotracheal tube, scar tissue production in the subglottis, just above the trachea and below the vocal cords, becomes severe to the point where the trachea is nearly completely obstructed with scar tissue, causing SGS patients to have difficulty breathing.

There are multiple etiologies or classifications of subglottic stenosis caused by events such as trauma, bacterial infection, viral infection, and cancer; however, the two most common are idiopathic and iatrogenic. Idiopathic onset occurs from an unknown cause, while iatrogenic onset follows a known injury or trauma to the region. Further, idiopathic affects primarily middle-aged women, while anyone is predisposed to iatrogenic stenosis. This is because intubated patients have a foreign body in their airway - an endotracheal tube - that causes constant irritation and injury.[1] One of the most common endotracheal tube injuries results from prolonged intubation in intensive care units of hospitals. This medical intervention is required in order for the patient to be able to breathe; however, there exists the substantial risk of continuous intubation causing a severe enough injury that induces SGS. Recently, the COVID-19 pandemic that began in late 2019 and rapidly spread from March 2020 onwards has caused an influx of chronically intubated patients in hospitals, leading to significant increases in prolonged intubation. This occurs because of viral infection of contaminated water droplets spreading SARS-CoV-2 throughout the respiratory system. Most patients with severe enough cases eventually require intubation or ventilation treatments.[1] However, the tubes these treatments require in the airway often injure it, stimulating excessive scar tissue cell growth to the point where the airway is mostly obstructed and the patient has difficulty breathing. Therefore, the rate of subglottic stenosis is on the rise, and with COVID-19 increasing the probability of stenosis progression, the interconnection between the two diseases must be investigated.

The current treatments for subglottic stenosis range from minimally invasive procedures, such as balloon dilation or stenting, to more invasive procedures; however, they are often unsuccessful, necessitating open surgeries like laryngotracheal reconstruction surgery (LTR) or partial cricotracheal resection (CTR). Although these more invasive treatments for SGS are moderately successful, the risks with these complex surgeries are worth noting. The biggest risk is that during these surgeries, the trachea can easily collapse due to structural integrity loss while physicians make incisions through the cartilage, which provides mechanical strength to the area.[2] In otherwise healthy patients with severe SGS, the airway is stiffer, which prevents this occurrence. In long-COVID patients with comorbidities, however, this is not the case, and so these types of procedures are far more dangerous. Additionally, as this is open surgery,

DOI: 10.36838/v6i7.12

bacteria and viruses in the airway can easily aerosolize and infect healthcare workers or other patients, ironically spreading the illness by trying to treat it, but it is worth noting that new diseases like COVID-19 require modifications to personal protective equipment and medical procedures, which would lower the risk of the virus spreading in such healthcare environments.

1.2. The Current State of SARS-CoV-2:

As for COVID-19, the most common preventative treatment is an mRNA vaccine that causes the patient's body to make proteins that are then translated into antibodies, which build up immunity to the virus.[3] After COVID-19 infection, however, patients who enter the hospitals require steroids, continuous monitoring, and ventilators for patients with breathing difficulties. However, even these methods have their drawbacks. The mRNA vaccines have to be stored at specific temperatures and can expire quickly. In August 2022, 42% of COVID-19 deaths in adults in the United States accounted for unvaccinated people, whereas a noticeably smaller 22% and 36% accounted for vaccinated people with the primary series and vaccinated people with the booster dose, respectively.[4] From this data, we can calculate that 58% of COVID-19 deaths in this demographic during this month were vaccinated, compared to 42% of these deaths being unvaccinated. This majority of vaccinated deaths shows that although the mRNA vaccine is helpful, it is only helpful to some degree in the potency of its immunity.

Similar to how both of these diseases are very important individually, their connection is lending to increased rates and intensities of the diseases, prompting this investigation into how the two are related. In this work, we will discuss how COVID-19 hospitalizations have increased the risk of subglottic stenosis and associated symptoms, with an analysis of novel, therapeutic treatments for disease management.

Discussion

2. Subglottic Stenosis in a COVID-19-Embattled World

2.1. Pathology and Disease Prevalence:

The symptoms of SGS are shortness of breath (dyspnea), higher mucous production, phlegm at the back of the throat, voice changes, and noisy breathing (stridor). The Meyer-Cotting grading scale is a common way to diagnose the severity of SGS in terms of lumen obstruction: Grade 1 is less than 50%, Grade 2 is between 51-70%, Grade 3 is between 71-99%, and Grade 4 is 100%, or full blockage of the lumen.[5]

The intensity of stenosis varies with multiple variables; however, the causes of this buildup delineate this stenosis into two etiologies, which are iatrogenic and idiopathic. Iatrogenic subglottic stenosis, as described above, is the formation of fibrotic scar tissue buildup due to an injury, generally from an endotracheal tube insertion or removal. This then causes massive inflammation typically two to four days days after the injury when immune cells such as macrophages secrete factors such as epidermal growth factors (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukins (IL), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and tumor necrosis factor-alpha (TNF-α).[6] These potent cytokines continue stimulating numerous neighboring cell types, such as fibroblasts, epithelial cells, endothelial cells, and stem and progenitor cells in the wound bed into a state of proliferation, differentiation, or activation.[7] Then, these cells all work together to produce the fibrotic scar that progressively occludes the airway. This buildup narrows the trachea and airway, making it difficult for patients to breathe. Resident fibroblasts, specifically myofibroblasts, produce excessive amounts of extracellular matrix and promote wound edge approximation by retracting the pseudopodia. This contraction of tissue slowly leads to wound closure.[7] Then, granulation tissue acts as an epithelialization area, creating an epithelial barrier to cover the wound. Under this protection, a scaffold of basal cells can migrate in and begin healing.

2.2. Risk Factors:

In 2021, the incidence rate of SGS had roughly tripled due to the increase of hospitalized patients on ventilators in hospitals bombarded with COVID-19.[5] There has also been a positive correlation between patients with long-COVID also developing post-intubation subglottic stenosis (PI-SGS) during their stay in the hospital. Moreover, if they have been on ventilators or re-incubated for at least 14 days, their chances of developing PI-SGS increase drastically.[1] As COVID-19 is very effective at spreading through transmission, healthcare workers and other patients are susceptible to developing COVID-19 and, in severe cases, a possibility of SGS, too.[7]

Interestingly, there are specific populations of people with an increased susceptibility to SGS, such as patients who are female, obese, smoke, and have a history of diabetes.[8] Although these populations have disproportionately high levels of SGS, this has expanded to include a few other vital demographics or characteristics. Specifically, patients who had or recently had COVID-19 in the past are now more prone to developing SGS while being intubated or on a ventilator for at least 14 days.[8] Furthermore, there has been an increase in African American patients suffering from SGS after receiving a COVID-19 diagnosis and intubation.[9]

2.3. Current Treatments and Associated Limitations - Open Surgeries:

Currently, there are many treatments for SGS. Some of them are open-neck surgeries, like LTR and CTR surgeries, commonly used in SGS patients with COVID-19. In an LTR surgery, surgeons make a vertical cut in the neck to access the airway from the outside, split the airway cartilage, and fill the space with a piece of the patient's rib cartilage to mechanically keep it expanded.[10] In a CTR surgery, the scar tissue and a large portion of the anterior cricoid cartilage are surgically removed, requiring the upward movement of normal and healthy trachea to replace it. However, these surgeries come with a big risk, as the patients can easily stop breathing with their trachea collapsing during the surgery. Also, since these surgeries are open-air, the bacteria in the throat can aerosolize and spread to other patients and the hospital staff, spreading SGS and COVID-19 instead of trying to treat them.[2] But in order to design more effective treatments, one needs to un-

DOI: 10.36838/v6i7.12

derstand the complex relationship and connections between COVID-19 and SGS.

3. Connecting COVID-19 to the Airway

3.1. Pathology and Disease Prevalence:

SARS-CoV-2 (COVID-19) has been especially prevalent since March of 2020, although the infectious disease was discovered in late 2019. As of 12:15 pm CET on June 21st, 2023, the WHO states that there have been 768,187,096 reported cases of COVID-19, out of which 211,331 have occurred in the past week.[11] The virus is a new, infectious disease that affects the respiratory system. It spreads through water droplets from an infected person to others nearby.[12] Specifically, when the infected person sneezes or coughs, the water droplets contaminated with the virus are inhaled by others within a close proximity of up to a six-foot radius. Once others have inhaled these water droplets with SARS-CoV-2, it spreads up the nasal cavity and throat lining cells and continues to damage healthy cells in the upper respiratory tract. In these cells, COVID-19's spike proteins on their capsid bind to the ACE2 receptor (angiotensin-converting enzyme 2), and the virus enters through cell membrane fusion or endocytosis.[13] The virus then travels to the cytoplasm, where its viral RNA is translated by the host cell's ribosomes into viral polyproteins. These are then bundled up into larger proteins with RNA-dependent RNA polymerase, synthesizing these larger proteins out of the original RNA intermediaries. These are then packaged into nucleocapsids to be secreted from the cells so that they can infect other cells. Altogether, the presence of this virus in the lower respiratory tract can cause comorbidities such as pneumonia and severe breathing difficulties. White blood cells commonly respond to the infection and leak into the lungs, filling the airway with debris and fluid, necessitating a ventilator.[12]

3.2. Risk Factors:

SARS-CoV-2 also has a plethora of risk factors that together encompass a high population, other than being within a close proximity to infected people. These include histories of smoking, diabetes, organ failure, acute liver injury, kidney disease, cardiovascular diseases, hypertension, hypoxemia, higher severity pneumonia, and obesity with higher BMIs.[14] Demographic risk factors are being of the male gender, being women in menopause and in higher ages, and being of African American ethnicity. These main risk factors alone encompass a large population, thus making many populations susceptible to contracting COVID-19.

3.3. Current Treatments and Associated Limitations - COVID-19 Vaccinations:

Currently, there are a few COVID-19 treatments. The first is mRNA vaccines, a preventative treatment to combat mRNA viruses. mRNA vaccines help human bodies by stimulating a response to the immune system, where the mRNA vaccine triggers cells to make antibodies from proteins.[3] This process works by the mRNA from the vaccine being injected into arm muscles, where they utilize the muscle cells' ribosomes and translation mechanisms to produce spike proteins with their mRNA. The cells then excrete the spike protein and make it bind to the extracellular side of their cell membranes. The immune system processes this spike protein as a foreign pathogen, causing the body to attack these cells. Then, the immune cells produce antibodies to fight against such spike-protein cells, both infected with the virus and touched by the mRNA vaccine.3 Once these antibodies are present, they lower susceptibility to getting sick when contracting the virus in the future, as the first line of defense has already been created by the immune system and can respond rapidly. However, a limitation of these vaccines is that their immune efficacy has been dropping over time as new boosters are needed, making their response to less fatal cases of COVID-19 less noticeable and less effective.[15] This could be explained by all the various mutant strains of SARS-CoV-2 that have arisen since the original outbreak in late 2019.[16] Oral antiviral treatments are another treatment in use, but they cannot be dispensed in various zip codes, decreasing access to this treatment.[17] Another procedural treatment for more severe cases is being in hospital incubation and ventilators, which was previously explored in this paper.

3.4. Current Treatments and Associated Limitations - Oral Antiviral Pills:

Another treatment being prescribed to patients with COVID-19 is oral antiviral pills. Paxlovid is a notable antiviral. Made by Pfizer, a biotechnology and pharmaceutical industry company that has also made vaccines for the virus, Paxlovid was engineered by combining nirmatrelvir and ritonavir, which are generic drugs.[18] Specifically, the nirmatrelvir helps prevent SARS-CoV-2 from recreating inside cells by inhibiting an enzyme. Previously being used to treat AIDS and HIV, the ritonavir helps bolster the potency of the treatment. A 2021 clinical trial by Pfizer revealed that COVID-19 patients who were treated with Paxlovid had an 89% lower chance of having their condition worsen with more severe symptoms and possibly death, compared to those in the trial who received the placebo antiviral. Although Paxlovid and other oral antivirals may seem like effective treatments in a quantitative measure, they have many side effects and rebound effects.[18] In the case of Paxlovid, it has countless side effects, such as an altered sense of taste, rashes, tightening of the throat, difficulties with swallowing and breathing, and much more. These antivirals also have many rebound effects anywhere from two to eight days after treatment. These are often identified through more positive SARS-CoV-2 tests, worsening symptoms of the virus, and, in rare cases, hospitalization.

4. Case Studies

4.1. Context and Data Collection:

To validate our hypothesis that SGS and COVID-19 are related in pathology and symptoms, we conducted a robust case study investigation into individual patients and explored their demographics, symptoms, and medical histories. We collected a total of 8 studies describing SARS-CoV-2 patients who had developed SGS and summarized their information in Table 1 below. In this table, we particularly analyzed the patient demographics (e.g. age, race, and sex), whether or not they had contracted COVID-19 before SGS and what treatments they had been given previously for COVID-19, other medical history, the symptoms that they presented with once they had developed SGS, and the types of assessments that were made to classify the SGS.

4.2. Analysis and Observations:

In this table, there is a mixture of both male and female patients. Additionally, patterns that were noted were that nearly all patients had contracted COVID-19 and had been intubated or implanted with tracheostomy treatments for COVID-19 in the past. Furthermore, many patients had a stenosis of Grade 4, or a stenosis where their airway was narrowed to two to four millimeters or stretched two-and-a-half to three centimeters along the length of their trachea.[9,24,26] Lastly, assessments done for these patients mostly included CT scans and bronchoscopies.[8,9,24-26]

Each patient who received a CT scan or bronchoscopy was analyzed for differences based on demographics, past medical history, or other variables reported in the table. The visualization of these reports is seen in Figures 6 and 7. In Figure 6, the CT scans in the sagittal plane revealed a narrowing of the airway as seen from the size at once spot in the airway.[9,24-25] In the axial plane, the airway was only seen as a small black dot in the center of the scan, indicating a narrowed airway.[24-26] Lastly, in the coronal plane, only Patient 5 received this view by the CT scan; however, it is more difficult to see the stenosis in this view compared to the other planes.[25] In Figure 7, Patient 2 had a completely occluded airway from scar tissue formation, whereas in Patient 3, a small hole that would allow for respiration could be visualized.[9,24] Lastly, Patient 4 has a narrowing of the airway but to a more minimal degree.[24] These findings on each of the CT scans and endoscopic images tell the same story and provide different views that confirm each other's findings.

Table 1: Demographic information, medical history, symptoms, and assessments done for patients with subglottic stenosis suffering from COVID-19.

Patient	Patient Demographics			Patient Medical History				Symptoms and Disease Findings			Types of Assessments	Ref
	Age	Race	Sex	COVID-19	Intubation/ Tracheostomy	Obese	Other	Dyspnea	Stridor	Other		
1	51	African American	Male	Y	Y	Y		N	N	Grade 4	CT-scans, endoscopy	9
2	35	African American	Male	Y	Y	Y		N	N	Grade 4	CT-scans, endoscopy	9
3	31		Female	Y	N	N		Y	Y	2-3 mm stenosis	Endoscopy, high-power micrographs, cross-sectional imaging	24
4	45		Female	Y	Y	N	Pneumonia	Y	Y	4 mm stenosis	Endoscopy, biopsy	24
5	71		Female	Y	Y	N	Pneumonia, pneumonitis, asthma, hypertension	Y	Y		CT scans	25
6			Female (75%) Male (25%)	N	Y (n=11) N (n=20)	Y (66%)		N	N		Endoscopy	8
7	35		Male	Y	Y	N	96% SpO2, trachial dilation	Y	Y	3 cm stenosis	CT scans	26
8	62		Male	Y	Y	N	85% SpO2, smoker, hypertension	Y	N	2.5 cm stenosis, wheezing	CT scans	26

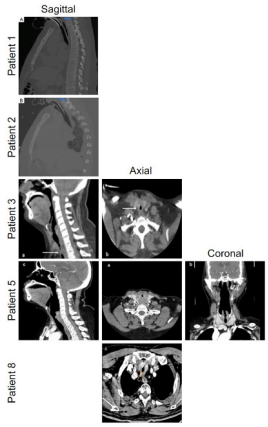

Figure 1: CT scans for patients 1-3, 5, 8 from Table 1. The CT scans how sagittal, axial, and coronal views of the stenosis. This figure is reproduced with Creative Commons permission.[9,24-26]

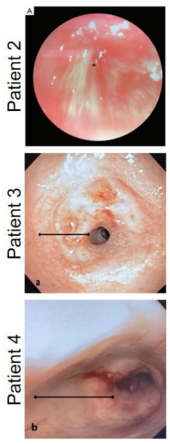

Figure 2: Endoscopies for patients 2-4 from Table1. The endoscopies reveal scarring and narrowing of the airway. This figure is reproduced with Creative Commons permission.[9,24]

5. The Rise of Subglottic Stenosis with SARS-CoV-2 and Novel Treatments:

The following three methods used to treat SARS-CoV-2 can sometimes induce injuries in the airway, specifically to the cells lining the lumen, that drastically increase inflammation. Thus, with this inflammation, the body's immune response to treat the injury is to grow scar tissue through fibrosis. As discussed earlier in this paper, this build-up of such scar tissue can block the airway. This calls for novel treatments to be investigated to circumvent the current limitations of what is currently employed in the clinic.

5.1. Antimicrobial Peptides:

There have been very few key advancements in the field of SGS treatments, with some being preventative and others for after the disease has been established in a patient's airway. One example of a therapy is a technology recently created by Aronson *et al*.[19] In this work, the researchers created antimicrobial peptide-eluting endotracheal tubes (AMP-ETs), which has been hypothesized to be a valuable and safe treatment in children with SGS. The tubes alter the bacteria in the airway when implanted, and the key to the platform is having a smooth coating, which helps them be more efficacious against SGS. The work refers to AMP-ET as Lasio/PLGA, indicating the AMP selected (lasioglossin) and the polymer carrier on the coating (PLGA). The researchers conducted an experiment and found that PLGA-coated ETs were less effective than their Lasio/PLGA counterparts. Aronson *et al*. also found that the Lasio/PLGA ET tubes exhibited viability of greater than 100% towards fibroblasts derived from the airway of pediatric patients; notably, 125% viability was observed with Lasio/PLGA ETs, suggesting fibroblast viability and proliferation is not only unhindered but also promoted by the coating and peptide release.

DOI: 10.36838/v6i7.12

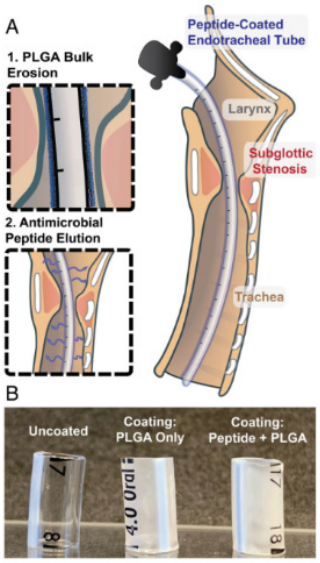

Figure 3: (A) Diagram indicating the placement of antimicrobial peptide-coated endotracheal (ET) tubes in the airway and where the ET tubes elute the peptides onto the fibroblast cells and bacteria on the stenosis. (B) shows the pictures of some of the different antimicrobial peptide coatings experimented with on the ET tubes. This figure is reproduced with explicit permission.[19]

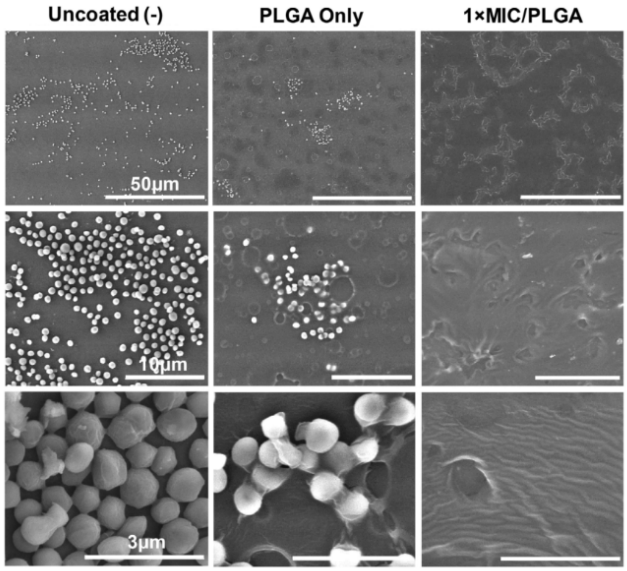

Figure 4: A collage of pictures from scanning electron microscopy of uncoated· PLGA only, and 1 x MIC/PLGA coated endotracheal (ET) tubes after they had been exposed to *Staphylococcus epidermidis* bacteria exposure for 34 hours. This figure utilizes magnification scales (2500x magnification for 50 μm, 10,000x magnification for 10 μm, and 50,000x magnification for 3 μm) to detail the advantage of 1 x MIC/PLGA peptide-coated ET tubes compared to other peptide-coatings to inhibit bacterial growth in the airway. This figure is reproduced with explicit permission.[19]

Aronson *et al*. recently followed this work up with another study that confirmed the effectiveness of utilizing AMP-ETs in the direct prevention of SGS.[20] Following coating procedures for the ETs coated with an AMP, the researchers studied the release into laryngotracheal complexes (LTCs) that had been excised from 6 mice for 10 days. This showed that the tubes could be implanted in the airway of a mouse and AMP would be released over a full week. Therefore, they put the coated ETs in the mouse tracheas of mice diseased with SGS and demonstrated that by the seventh day after disease trauma, the severity of the SGS had rapidly reduced. Further analysis revealed AMP was released at a rate of 1.16 μg/day, inhibiting the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria, and was again biocompatible toward airway fibroblasts and epithelial cells. An interesting finding the group identified was that the AMP-ETs decreased the immune responses of T cells and macrophages, reducing the SGS overall. Besides AMP-ETs, current research has also focused on drug-eluting ET stents, and nanoparticle and microparticle-delivered therapeutics.

5.2. Rapamycin:

Some of the different polymers used to make these devices are PLGA, PLLA, and PCL. The polymers are different in chemical structure, but physiologically differ in degradation rate. PLGA degrades faster than PLLA, which degrades faster than PCL.[19] Any combination of the different polymers is an attempt to change the degradation rate. In addition, PLGA is more hydrophilic than PLLA and PCL, making it easier to incorporate more hydrophilic drugs than hydrophobic ones. Similarly, PCL can coat hydrophobic drugs better. They also have different mechanical properties, but their mechanical strength follows the same trend as degradation; PLGA is the weakest, then PLLA, and then PCL, which is the strongest polymer.

Some of the additional research in recent years in drug-eluting stent treatment includes the therapeutic, rapamycin. Duvvuri *et al*. produced airway stents out of PLLA-PCL, which are more structurally stable than the commonly used PDLGA stents.[21] Furthermore, these PLLA-PCL stents can elute drugs for over six weeks and can elute much stronger drugs to deal with drug-resistant bacteria (30% rapamycin with PLLA-PCL stents, versus less than 1% with PDLGA stents). These enhanced specifications of PLLA-PCL drug-eluting stents also enhance their capacity to inhibit the growth of fibroblast scar tissue that arises in SGS.

5.3. Lidocaine:

Another fascinating study conducted promising research in making lidocaine-eluting ET tubes and stents. Topical lidocaine treatments are used on patients' bodies, often bringing numbness or pain-relieving feeling during medical procedures, cuts, and allergic reactions.[22] Regarding utilizing this drug for ET tubes, Lu *et al*. utilized lidocaine to easily and uniformly coat the ET tubes, causing SGS occurrences to smallest mucosal edema area percentage and smallest mucosal thickness in the trachea, in the test conducted on rabbits.[23] Furthermore, the researchers found it to be the most effective when lidocaine was eluted along with a PLGA1000 polymer. Although the advancements are promising for COVID-19-induced SGS, these novel treatments are still being tested and experimented with to better understand their ability to fight it.

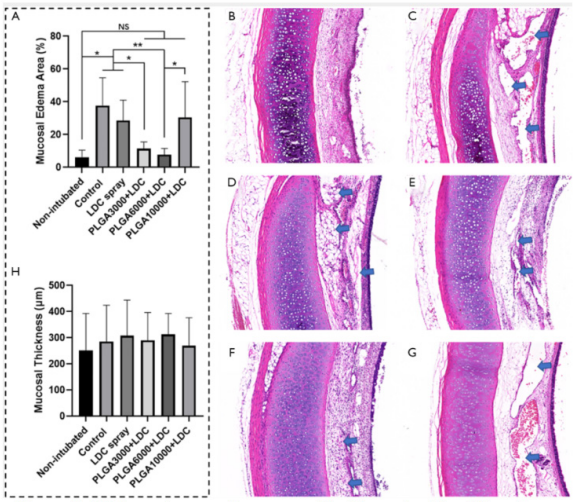

Figure 5: (A) Area of mucosal area quantified for each of the different treatment conditions. (B-G) Each of the different treatment conditions, ranging from non-intubated to PLGA1000+LDC in the same order as Panel A. (H) Quantified thickness of the mucosal layer between all treatment conditions. This figure is reproduced with Creative Commons permission.[23]

5.4. Novel Therapies - Commentary:

While antibiotics like rapamycin and anesthetics like lidocaine have been used before in medical treatments, they both have been known to cause an array of side effects, potentially setting patients back on the COVID-19-SGS recovery pathway. However, since AMPs have both naturally found and synthetically produced forms, the chances of side effects could definitely be reduced with this treatment by not being detected by the immune system as a foreign agent. The body will have a lowered chance of rejecting a treatment when it is biochemically made up of similar molecules with similar structures as some already found in the body, being proteins and specifically, antimicrobial peptides. Thus, it is likely that antimicrobial peptides may be the treatment with the highest chance of effective treatment.

In summary, all three treatments are well on their way to addressing and potentially solving the correlation of SGS from SARS-CoV-2, even though it is worth noting that these treatments have been tested only on animal test subjects. Thus, it will be interesting to see how these fair when applied to human subjects, although this requires more testing, as well as ethical, medical, and legal approval processes. It is likely that more potential treatment options may appear in the field as well, especially as COVID-19's impacts are further discovered.

■ Conclusions

In conclusion, SARS-CoV-2 treatments can induce subglottic stenosis by injuring and inflaming the airway, causing the body to stimulate the growth of fibrous scar tissue. This buildup of such scar tissue narrows the airway, leading to subglottic stenosis with a very obstructed airway where patients exhibit severe symptoms such as dyspnea, stridor, and breathing problems. Although COVID-19 treatments could be as simple as Paxlovid antiviral pills and mRNA vaccines, patients with severe or chronic COVID-19 on ventilators requiring re-intubation have been increasing the incidence of SGS. Ever since late 2019 and early 2020, when SARS-CoV-2 struck the planet, there has been a growing correlation between COVID-19 and SGS. With COVID-19 on the rise and with it, SGS, the conventional treatments such as LTR and CTR surgeries that have many risks and complications must be revised. Therefore, it is worth investing more time, effort, research, and experimentation into novel therapies for SGS to help prevent COVID-19 patients from developing SGS, such as drug-eluting ET tubes, stents, and other controlled drug delivery platforms.

■ Acknowledgment

I attest that the ideas, graphics, and writing in this paper are entirely my own, and that graphics that come from other sources have granted me with either explicit permission or Creative Commons abilities to use them, following proper citations. I sincerely thank Mr. Matthew Ross Aronson from the University of Pennsylvania and the Children's Hospital of Philadelphia, and Indigo Research for their mentoring and guidance on the final research paper.

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