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Inclusion of steps to enhance mucus clearance may provide benefit for symptomatic COVID patients by reducing total viral load, time to recovery, risk of complications and transmission risk

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Abstract

The COVID pandemic brought healthcare systems close to the breaking point and stimulated research which has led to an effective vaccine, but no reliably effective antiviral medication to treat active infection. A prioritization of transmission risk reduction has emphasized patient isolation and personal protective equipment (PPE) for healthcare workers and others. Clinical management improved somewhat with inclusion of corticosteroids, as well as a few antivirals, but remained primarily supportive in nature [1]. Another form of treatment, mucus mobilization has not been perceived as a priority for preventing or treating disease. Furthermore, proning ventilated patients is practiced intermittently and is not prioritized in managing ventilated patients, as it is rarely recommended. Mucociliary clearance (MCC) forms the backdrop for a mucocentric perspective on COVID and other respiratory conditions. While widespread objective measures of MCC and mucus burden are lacking, but it is likely these factors play a significant role in infection risk and variability of clinical course. The identified high-risk groups share a feature of impaired awareness and response to the presence of excess mucus [2]. While further research is needed, safe and cost-effective steps based on improving MCC are available for immediate implementation: these include strategic body positioning, upper respiratory care, refinement of cough technique and airway hydration.

Introduction

The term immunity encompasses a vast array of cells and molecules which interact with the environment. There has been an explosion of knowledge in the past 50 years. The year 2021 has witnessed a world-wide scientific and humanitarian effort to defeat the COVID-19 pandemic. We owe much to Dr. Fauci and the worldwide scientific effort which has made monumental additions to knowledge of the internal immune system. Our hopes now rise as COVID vaccine distribution continues - a direct result of research and development on the internal immune system.

Adaptive immunity and the internal immune system have received a copious amount of attention during the pandemic. While, in no manner or fashion is this paper intended to diminish the efforts and accomplishments that have come about as a result of the research related to COVID. With that being said, the focus of this paper is to share a mucocentric perspective as one component of inflammatory respiratory conditions. To that end, rather simple steps to enhance MCC may prove surprisingly beneficial.

Scientists warn us that epidemics with new strains of virus are inevitable, and vaccinations will never be a cure-all. As a result, immunization by vaccine may lose effectiveness over time, as vaccination may have reduced effectiveness against any mutated strain of COVID-19 [3]. Although unlikely to create media headlines, we should remind ourselves of the first line of respiratory immune defense which is all too often taken for granted. We hope others will join Dr. Fauci in calling for more research to understand and improve our natural immune resistance.

"FIRST LINE" of innate immune defense: The mucus layer

Mucociliary clearance

The importance of the first line of respiratory immune defense is often overlooked, as it acts in the background, being forgotten as a major system for bodily defense against pathogens. When we breathe, outside air flows through our nose or mouth into a system of branching tubes until reaching the alveoli [4]. While it might be overlooked, the thin layer of mucus which coats our nasal and bronchial passageways catches hundreds of pollutants every day. It is through this continuous layer of mucus that most harmful pathogens that enter our airway are brought upward to where they are coughed or swallowed, eliminating their potential infectious possibility [4].

Two cell types work together to form a protective layer over the upper and lower respiratory systems, ciliated and secretory [5]. The nasal passages, sinus cavities, main windpipe, and the multitude of branching bronchial tubes carrying air to and from lung air sacs where oxygen and carbon dioxide are exchanged. Under the regulation by immune factors, goblet cells and mucus glands steadily produce a clear thin mucus with a glycoprotein profile which contributes to optimal

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viscosity [4]. Most numerous are the surface epithelial cells whose hair-like cilia protrude into the overlying mucus layer. In health, these tiny oars beat in a relentless and coordinated fashion, sweeping mucus out of the lower bronchial passages, into progressively larger passages and eventually out of the lungs. It is when disease arises that this system becomes compromised, as stagnated respiratory mucus creates opportunity for infection and further complications [5].

Infected wound analogy

Consider an open skin wound which has become infected. Don't we take care the wound is clear of dirt and other debris? If there is pus formation, don't we soak, clean and change the bandage as often as needed? And finally, if there is formation of hard, dry scab, don't we soak in warm, soapy water to loosen and then gently wipe it away? We do all these things because we know clean tissue with proper moisture level will heal most quickly. According to some wound experts, soaking and cleaning are more important than antibiotics. Does it make sense to apply the same principles for respiratory infections?

The mucocentric perspective

Why the mucus connection is easily overlooked

Often, symptoms of dry cough and nasal congestion without rhinorrhea may be explained by the presence of mucus too thick to move. Patient and/or caregivers perceive mild nasal or chest congestion as normal, inconsequential, and not needing medical attention. Although understandable, concern for reducing transmission risk discouraged healthcare providers from using aerosol treatments as an effective COVID treatment, as some research shows viral particles may remain in aerosolized for up to 3 hours [6]. Because of this, coughing and other steps to promote mucus mobilization are largely absent from treatment protocols. As seen in many patients, lingering symptoms often occur and can lead to reduced mucus clearance. Upon improvement, patients may fall back into a state where they experience hindered awareness and responsiveness to bronchial mucus reservoir [5].

Rationale to support a significant mucus component

Autopsies performed early in the pandemic in Wuhan describe a majority finding of abundant pasty mucus throughout the bronchial passages [7]. Anecdotally, ICU personnel report that in several cases, acute occlusion of endotracheal tubes (ETT) due to mucus plugging resulted in urgent replacement of ETT, as one study reported that 28 of their 110 ICU patients needed the procedure redone. Upon evaluation of the removed ETT, characteristic "sloughed tracheobronchial tissues and inflammatory cells in a background of dense mucin" was observed, which lead to decreased oxygenation and ventilation within patients [8].

Even for some patients once they have recovered from the illness, it is suggested that continued hypersecretion of thick mucus may appear to be a persistent long-term symptom of the illness [9]. Overall, while data regarding the condition is still emerging, it appears that mucus hypersecretion both during illness and post-recovery are implicated as factor [9]. This component of the illness warrants further investigation into means that would aid to limit both the level of mucus secretion, as well as mucus mobilization within patients. It is also suggested that increased awareness regarding mucus retention should be made to individuals apart of high-risk groups, as tolerance and decreased awareness within these patients may contribute to causes of disease [10].

"Dry mucus" connection: why the winter spike?

Influenza and other respiratory virus infection are more frequent during winter seasons when decrease in outdoor temperature inevitably leads to reduced humidity level of indoor air [11]. In one cohort study of 50 different cities published in June of 2020, correlates between lower temperature and humidity rates were found in areas in the 30° N to 50° N corridor [12]. These similar weather patterns found that infection rates were highest in these areas, as lower temperatures ranging between 41°-51.8° F, lower specific humidity and lower absolute humidity were observed [12]. Through the data collected, researchers noted that the behavior of COVID-19 as it relates to seasonality acts similar to common seasonal respiratory viruses, suggesting that temperature and humidity are also implicated in the number of reported cases.

This phenomenon was also demonstrated in the laboratory. One study showed mice raised in low humidity demonstrate increased risk of infection by a SARS-like virus. Reported data showed that mice housed in 20% relative humidity (RH) more disease outcomes, lower body weight and longer survival times than mice housed in 50% RH [13]. Furthermore, impaired mucocilliary clearance, antiviral immunity and tissue repair was noted in the study [13]. This invites the idea in which virus captured on dry, slow moving or stagnated mucus would be more likely to achieve attachment and penetration into respiratory epithelial lining. The opposite effect was seen in the control group, where mice raised in normal humidity were shown to maintain a mucus layer that enabled virus capture and clearance, eliminating the opportunity for infection [13].

Pathophysiology: A mucocentric perspective

Although COVID virus is transmitted in a manner like other respiratory viruses, the symptoms and wide-ranging immune responses are quite different from that of other respiratory viral infections. Airborne transmission from an infected individual to a host is the sine qua non for spread of viral infection. COVID virus is transported in the exhaled breath of an infected individual per respiratory droplets [14]. Airborne respiratory droplets and aerosol containing virus encounter the host respiratory mucus layer. If virus is swept away via mucociliary clearance before host cell attachment and penetration takes place, infection is prevented [15]. In contrast, a virus landing on stagnated mucus layer is provided with an increased opportunity for attachment to membrane receptors and penetration into host cells [15]. This may lead to excess mucus accumulation, contributing to shortness of breath, hypoxia, and eventual respiratory failure [14].

A virus "reservoir" in retained mucus and increased risk

Upon death of infected host cells, thousands of viral particles are released into adjacent interstitial space and overlying mucus layer [15]. This results in increased exposure to adjacent airway cells and promotes local spread of infection within host. Viruses accumulated in the overlying mucus layer are picked up in respiratory droplets that are expelled with cough, or normal breathing [15]. Finally, it is hypothesized that the toxic soup of inflammatory cells and cytokines within stagnated mucus impair recovery of airway cells, contribute to acute respiratory distress syndrome (ARDS) pathogenesis and protracted stimulation of the systemic immune system.

Mucus tolerators: A vulnerable hidden phenotype

Reduced awareness and responsiveness to increased respiratory irritation and mucus accumulation can be easily overlooked as a significant factor of causing disease. A described "tolerance" of excessive bronchial mucus is usually observed in individuals with comorbid conditions, such as those with COPD, asthma, and cystic fibrosis [5,10]. While some patients may describe their cough as only "throat clearing", the driving force behind the action may be more serious than

they believe [10]. For many otherwise healthy appearing individuals, a degree of respiratory congestion may be viewed as baseline for them. Signs and symptoms of this may appear subtle, such as cough, rhonchi and wheezes, though physical exams warrant no further investigation, as patients may describe their symptoms as baseline. While it may be difficult for some to perceive, it is important to recognize both the frequency and duration of coughing that occurs, as it provides important details as to the mucus retention that individuals are experiencing [10].

Treatment: A mucocentric perspective

To achieve optimal recovery, especially in individuals with COVID-19, prioritization of mucus hydration to reduce mucus viscosity, along with other steps to enhance mucus clearance of upper and lower respiratory passages should be emphasized. Simultaneously, transmission reduction measures must also be enforced as to not cause further spread of viral particles.

Upper respiratory care: Reducing complications, transmission risk and duration of infection

In a pilot study conducted in 2019, researchers evaluated the combined use of hypertonic saline nasal irrigation and antiseptic gargling for treatment of individuals prior to URTI onset. Compared to the control group, individuals in the experimental group were found to have lower duration of illness by 1.9 days, 36% reduction in the use of over-the-counter medications and 35% reduction of transmission to household contacts [16]. Other studies targeting the specific use of antiseptics also showed efficacy towards herpes virus. Upon evaluation of data collected, total recovered viral particles were not quantifiable when measured 30 seconds post-rinse, as compared to the control group. The experimental group was also noted to have significant reduction in viral load when evaluated 30 minutes post rinse, while the control group did not [17]. Overall, nasal irrigation, saltwater nasal rinse with, and without, oral gargling with antimicrobial mouth washes has shown to reduce clinical severity, symptom duration and may aid in preventing upper respiratory infections [16-19].

As the first point of contact for infectious particles, the lining of the upper airway passages should be regarded as a vital area for initial prevention of COVID-19 infection [18]. Although not definitively determined, it is likely the nasal membranes that are the initial contact point of infection [18]. Enhancement of mucus layer integrity and mucociliary clearance offers the exciting possibility of preventing initial infection and, if infected reducing viral load and risk of transmission [16-19]. While awaiting further study, it would seem reasonable to encourage these techniques during the current COVID-19 pandemic and that should receive more attention as a means of treatment for COVID-19 patients.

Cough: An understudied technique to improve mucociliary clearance

Coughing is most often considered as a symptom triggered as an involuntary response to stimulation of nerves along the respiratory tract [20]. Deep inspiration before a typical cough drives dry room air deep into the bronchial passages. But as seen throughout individuals, spontaneous coughing is highly variable between, as cough threshold and cough mechanics can differ. Typically, a deep hard cough is sometimes needed to clear mucus but, if performed too frequently, could cause an ineffective effect as mucus clearance is hindered [20].

Coughing can be viewed as cleaning away the excess bronchial mucus accumulation which occurs in nearly all inflammatory and infections conditions. A proposed strategic cough technique and scheduled cough sessions invite us to consider benefits which follow intentional steps to mobilize mucus for recovery/restoration of mucociliary clearance. As previously stated, as improper coughing way be ineffective towards effective clearance of mucus, training of patients on proper techniques serves to achieve this goal.

A described technique referred to as "huffing" provides the optimal respiratory pressurization to achieve mucus clearance, as well as avoid injury or ineffective clearance. Huffing is a maneuver that is completed in mid to low range lung volumes, as it creates equal pressure points per equalization of intraluminal and extraluminal pressure that reach deeper into the respiratory passages to allow mucus mobilization [21]. Studies regarding this topic have found that peak inspiratory flow rate should be 10% at the minimum for mucus mobilization to occur. Furthermore, the study also found that peak expiratory flow rate should exceed 30-60 L/min in order to achieve mucus loosening to become mobilized [21]. Other techniques that are often employed with cystic fibrosis (CF) patients such as autogenic drainage (AD), as well as other techniques such as positive expiratory pressure (PEP) therapy and oscillating positive expiratory pressure (OscPEP) are established treatments used in mucus clearance within individuals [21].

In further mechanisms to induce effective coughing, research has shown that high-frequency airway clearance (HFCWC) devices can create airway volume changes ranging from 15-57ml, as well as increases in flow rate up to 1.6L/s [22]. These devices act by using periods of constriction on the chest at different frequencies, along with time being allowed for coughing. Through this technique, mucus mobilization through lower force coughing is able to be achieved within individuals who experience hypersecretion of respiratory mucus [22].

Overall, the data regarding coughing techniques shows that deep, hard coughs do not always achieve the mucus clearance that is desired within individuals [21]. Because of this, proper education for patients regarding optimal techniques should be reinforced. Through patient instruction, proper mucus mobilization could be achieved. This also serves to ensure patient safety, by limiting the amount of hard coughing that is completed as to avoid the possibility of lung damage or rib fracture [23].

Humification of air for disease prevention and mucus mobilization

A number of published peer reviewed studies have shown the potential benefits of humidified air as a mechanism to limit disease. Airborne transmitted bacterial and viral populations have been shown to have significantly lower survival rates within areas of humidity ranging from 40-70% [24]. Experimental data from a 2010 study regarding influenza survival found that use of a portable humidifier with a 0.16kg of water per hour output led to a decrease survival rate from 17.5-31.6% [25]. Furthermore, mite and fungal populations have been shown to be affected by humidity as well, as population sizes decrease when humidity levels do not exceed 60% and 80%, respectively. Therefore, suggestions from one article state that a "majority of adverse health effects caused by relative humidity would be minimized by maintaining indoor levels between 40 and 60% [24]. Overall, the data regarding the use of humidifiers within enclosed spaces provides promising data, warranting further investigation and possible implementation for the use of evaporative or steam humidifiers as a means of disease mitigation.

Correlates between temperature and humidity also appear to affect mucus mobilization within individuals. One study using a laboratory

trachea model showed that decreases in air temperature from 37° to 34 or 30° at 100% RH lead to a decrease in ciliary beating frequency (CBF) [26]. Additional studies have also backed this idea, as levels of mucus spinnability and CBF are associated with decreases in temperature and RH [26,27]. Benefits regarding nasal canula users have also been reported, as mucus clearance and prevention of atelectasis formation serve as the most vital factors. Thus, the data suggest that the role of humidity may serve to be dual purpose, as instances of infections particle survival rate, as well as mucus mobilization are affected.

Patient positioning

Another proposed mechanism for safe and effective treatment would be changing of patient positioning in bed. Prone positioning (PP) works to recruit alveoli to improve ventilation/perfusion matching [28]. Through this mechanism, increased pulmonary perfusion and bronchial mucus clearance can be achieved. In past data collected prior to the pandemic, clinical trials have shown in over 70% of intubated patients experiencing non-COVID-19 related ARDS, oxygenation rates increased ranging from 34-62% [28]. Furthermore, reductions in instances of mortality and ventilator associated pneumonia (VAP) have also been observed in PP patients [28].

While past data suggest advantageous outcomes for PP patients, emerging data regarding intubated and non-intubated COVID-19 patients also suggests the same outcomes. In one study published in May of 2020, researchers found that alternating between supine and prone position was correlated with higher lung recruitability in intubated patients when compared to supine alone [29]. Other studies referencing non-intubated patients, researchers identified 10 hospitalized COVID-19 positive individuals who were at high risk for intubation due to increasing oxygen requirements. Patients were asked to alternate between the supine and prone position throughout the day. It was found in the study that oxygenation rates vastly improved within 1 hour of PP from 94% to 98% on average [30]. Furthermore, rate of breathing had also decreased as respiratory rates decreased from 31 to 22 breaths per minute, as patients reported decreased amounts of dyspnea [30]. Following the study, 80% of the patients who partook went on to not require intubation procedures, due to reported improvement after PP. While the researchers acknowledge that limitations to the study included the smaller sample size, they state that the rapid increase in oxygenation rates provides meaningful data which suggest future studies should be completed regarding the topic. As previous studies prior to the pandemic have shown that patients who experience ARDS which were placed in PP reduced mortality rates from 32.8 to 16.0% [31], it would seem reasonable to introduce this technique more often amidst the current pandemic as an additional treatment measure.

Mucus mobilization in high-risk individuals

Research conducted has shown that individuals newly tracheostomized patients experience mucus airway drying, due to the normal humidification process being bypassed [32]. As this has become a common procedure undergone in COVID-19 patients who have undergone prolonged ETT intubation, awareness regarding the differences in the mucosal layer post-operatively are relevant as to not cause further complications [32,33]. Rates of suctioning procedures to remove stagnated mucus are often undergone which increase the rate of lower respiratory tract infection and mucus obstruction [32].

Studies conducted pre-pandemic have shown that the delivery of heated, humidified air instead of cold nebulized air leads to increased CBF and mucus clearance within individuals [32]. The same study also found that rates of suctioning procedures dropped from 5 to 3 [32]. While current treatments available exist, such as heat-and-moisture exchangers (HMEs), which retain some of the humidity from expired air, there are further techniques such as ones which airflow through heated water prior to inspiration that can be used to help humidity the mucosal layer within tracheostomy patients [32]. While no data regarding the topic is currently published, it is hypothesized that this is analogous to individuals who sleep with their mouth open, as it creates a similar effect as inspiratory airflow is diverted from the nasal passageway. Based on the data it seems reasonable to that further research be conducted, as changes in the humidity levels for newly tracheostomized COVID-19 patients may prove to be beneficial.

Final comments: mucolytics for mucus hypersecretion and stagnation

A final option for treatment of mucus hypersecretion comes in the form of mucolytic use. One cough suppressant bromhexine hydrochloride has been noted as being a potential agent for limiting COVID-19 related mucus hypersecretion per inhibiting TMPRSS2 and viral entry [34,35]. Other agents such as n-acetylcysteine (NAC) has been shown to inhibit replication per the p38 MAPK system [35]. Although the data is still emerging regarding the use of mucolytics within COVID-19 patients, is it the hope that future studies will provide more data showing patients within COVID-19 may also benefit as well.

Patient education, instruction and motivation

Provider instruction and encouragement

At the core of safe and effective treatment, sufficient provider instruction and compliance is critical for aiding patient recovery. Furthermore, enthusiastic delivery of the message from a provider should also be emphasized. While some might view it as excessive, detailed explanation, instruction and demonstration with an interactive style should be employed for patient education. Through this, it is the goal to encourage patients to initiate mucus clearance through the strategies outlined.

For providers, fatigue, discouragement, and distraction by other issues can deplete energy for detecting and addressing issues with mucus buildup. Keeping the mantra in initiate mucus mobilization can remind us to pay attention to mucus levels. Finally, helping patients to recognize positive signs, such as lessening of shortness of breath, increased oxygen saturation, return to normal heart rate, and reduced involuntary cough should be emphasized to patients as positive reinforcement measures towards recovery.

Patient instruction and pep talk

- Examples of instructions and explanations to patient:

Nasal:

- Patients may be or may not be aware of nasal symptoms, such as congestion lack of smell, but nasal membranes are most likely source of COVID viral attachment and infection. If there is nasal membrane congestion, the stagnated mucus be a site for viral replication and become a reservoir as a result of the separation from the zone of safety away from the body's internal immune system [35].
- Steps to enhance nasal mucus clearance could be a path to reduce viral load spread within the body and transmission risk.

- Use of nasal rinses and gargling with antiseptic solutions are methods to improve mucus mobilization and accomplish reduction of viral load [16-19].

Cough:

- Not necessary to clear it all once.
- Think of a push broom… steadily sweeping excess mucus from the deep passages toward the central main windpipe. From there, it is much easier to cough out.
- A cough which triggers a reflex throat swallow is not dry. In fact, it proves that mucus was brought up out of the lungs.
- If mucus does not reach the lower throat area, it may mean the bronchial mucus is 'too dry to move' and the steps to enhance hydration of inspired air should be pursued even more diligently.

Words of encouragement:

- You are going to have to fight to get better. With COVID infection, you feel lousy, tired, achy, and often lonely. It is tempting to just rest and wait for the illness to run its course. The internal immune system is a great and wonderful thing but sometimes… not good enough. We can help our immune systems to fight with steps that are not too demanding. You can speed the recovery system by "getting that junk out of your lungs."
- Pay attention and watch for those signs, maybe slow at first, telling yourself. You're getting better! You are going to make it!

Conclusion

In conclusion, mucus hydration and mobilization are unlikely to become popular topics for treatment of ARDS and COVID-19 related syndromes. But for now, while we await further research, we hope healthcare providers will take the extra time to instruct and encourage patients on effective and simple treatments. If implementation of these concepts reduces severity of patient symptoms and increases treatment outcome, the benefits of the steps outlined could help to become standard of care. Establishing and maintaining a healthy mucosal environment, which includes hydration of the overlying mucus layer may offer benefits in the realms of prevention, reduced transmission risk and reduced overall viral load.

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