



## Systematic Review

# 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 PPE for healthcare workers and others. Clinical management improved somewhat with inclusion of corticosteroid but remained primarily supportive in nature. 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. Objective measures of MCC and mucus burden are lacking, but it is likely these factors that 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. 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. Some rather simple steps to enhance MCC may prove surprisingly beneficial.

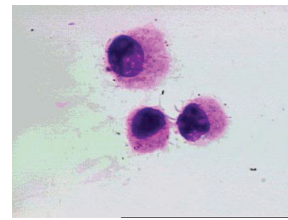
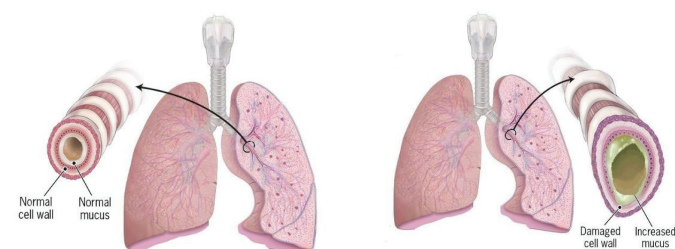
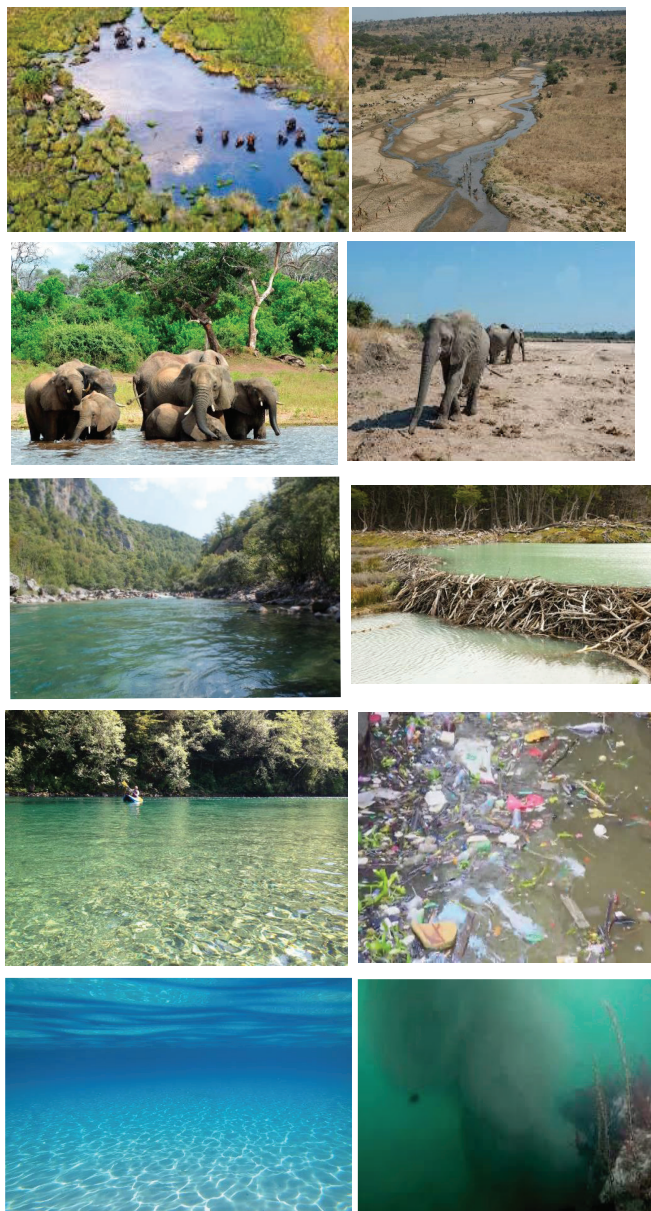
Scientists warn us that epidemics with new strains of virus are inevitable and vaccinations will never be a cure-all, and as a result immunization by vaccine may lose effectiveness over time, as vaccination may have reduced effectiveness against a mutated strain of COVID [1-3]. Although unlikely to create 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 and Dr. Yamasaki in calling for more research to understand and improve our natural immune resistance.

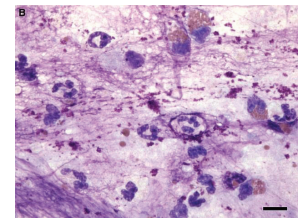
## “First Line” of innate immune defense: The mucus layer

Consider the image of how a flowing stream or river supports life and clears contaminants and debris naturally.

### Water: Ubiquitous in the natural world and our bodies



Normal: occasional squamous epithelial cells from upper airway inadvertently contaminate an otherwise acellular specimen.



“Dry”, “sticky” bronchial mucus contains immune effector cells reflect lower respiratory inflammation specimen.

## 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. While it might be overlooked, the thin layer of mucus which coats our nasal and bronchial passageways catches hundreds of germs, allergens and pollutants every day [4]. 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.

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 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.

## 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. 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.

### Rationale to support a significant mucus component

Autopsies performed early in the pandemic in Wuhan describe a universal finding of abundant “pasty” mucus throughout the bronchial passages [2]. Anecdotally, ICU personnel report little mucus return with appropriate catheter suctioning when inadequate ventilation requires re-intubation as the previous endotracheal had become “completely plugged with mucus” [6]. For some patients, the continued production of thick mucus continues long after resolution of acute symptoms [7].

No unifying theme of impaired adaptive immunity has been identified across the high-risk groups. Individuals with bona fide immune deficiencies such as patients receiving conventional chemotherapy, “Biologics” or HIV have not shown increased risk for COVID infection. Without objective evidence, high-risk groups do not share defect of the internal immune system, is it within reasonable speculation that these groups share symptoms decreased respiratory awareness and excess mucus tolerance when compared to baseline.

### “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 [7]. COVID’s origination during Wuhan’s winter months, daily new infection rates were found to be highest on days when colder, drier outside air may have contributed to reduced indoor humidity per computer reported via [7]. This phenomenon was demonstrated in the laboratory. Mice raised in low humidity demonstrate increased risk of infection by a SARS-like virus [8]. 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.

### 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. 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. In contrast, a virus landing on stagnated mucus layer is provided with an increased opportunity for attachment to ACE 2 membrane receptors and penetration into host cells. This may lead to excess mucus accumulation, contributing to shortness of breath, hypoxia, pneumonia, and eventual respiratory failure.

The final opportunity for prevention of infection rests on the speed and vigor of host early innate immune response. Quantification of the behavioral components of the innate immune system is difficult. Nonetheless, impairment of respiratory defenses, increased cough threshold and reduced recognition and response to early symptoms could be anticipated for high-risk groups, as incidence of events such as mouth breathing in sleep contribute to mucus drying. This as a result may further contribute to inhibition of mucus clearance in individuals.

### 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 [9]. 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. Finally, it is hypothesized that the “toxic soup” of inflammatory cells and cytokines within stagnated mucus impair recovery of airway cells, contribute to 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 populations of elderly, infirmed and those with significant physical and/or cognitive impairment. The comorbidities of diabetes mellitus and hypertension may be conceptualized as associated but not causative with respect to infection.

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 nasal voice quality, throat clearing or occasional wet cough, though physical exams warrant no further investigation, as patients describe their symptoms as “normal for me”. Cough, when present, is less frequent, less forceful and less sustained than would be appropriate to the amount of chest congestion. It is hypothesized that these individuals are more likely to eventually require medical attention although recognition of worsening is invariably delayed. Finally, when treated, the return to their previous baseline is erroneously considered as a sufficient and satisfactory recovery.



## Treatment: A mucocentric perspective

To achieve optimal recovery, especially in individuals with COVID, 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. A common misconception that might arise is the belief that increasing fluid intake will lead to hydration of respiratory mucus, but this is not true. Humidification of air in the form of room vaporizers, personal vaporizers, “steam rooms” or “croup tents” are effective measures at hydrating the mucus layer [10].

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

Nasal irrigation, sea water nasal rinse with, and without, oral gargling with antimicrobial mouth washes reduced clinical severity and symptom duration [11,12], prevented upper respiratory infections [12,13] and provided benefit for individuals infected with rhinovirus, enterovirus, influenza A virus, and coronavirus families and reduced transmission to other close contacts [13].

Meiller et al, among others demonstrated gargling antiseptic solutions reduced HSV viral load [14]. WHO has also stated that antiseptics show to be effective in deactivating COVID-19 viral particles [15]. While awaiting further studies, 2017 WHO has recommended simple steps for prevention and treatment of Ebola, Zika virus and emerging Coronavirus infections [15]. 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.

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 [11]. Although not definitively determined, it is likely the nasal membranes that are the initial contact point of infection [11]. 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 [11-15]. By enhancing mucociliary clearance, the critical step of viral attachment may be prevented.

### 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. 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 undesirable “drying effect” upon proximal and distal bronchi.

Coughing can also 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 an obvious impediment to recovery/restoration of mucociliary clearance [16]. Furthermore, tidal breathing and gentle exhalation (corresponding to FRC) followed by a medium-force cough with attention to avoid the pre-cough inspiration of room air may prove as a beneficial practice [17]. This maneuver would be encouraged every 2 minutes during a strategic cough session. By performing this, the lower cough force avoids the issues of fatigue or chest wall discomfort from muscle strain or possibility of rib fracture. Thus, with a cough now less strenuous and less conspicuous, it can be performed at will outside the scheduled cough sessions. It is also suggested that further treatment options and research be completed to evaluate the beneficial uses of high frequency chest wall oscillation devices, as studies show they can improve mucus clearance within dysfunctional pulmonary systems [5].

### Patient positioning

Another proposed mechanism for safe and effective treatment would be changing of patient positioning in bed. Positioning enlists gravity to assist in clearance of bronchial mucus and alveolar fluid. Sequential supine, right and left decubitus and prone positions achieves downward orientation of bronchi from each area of the lungs. These techniques have been shown to be effective in both non-intubated and intubated patients, as downward orientation of bronchi aids in mucus clearance from the lungs. For moderate, severe and critically ill patients, appropriate monitoring would guide interventions to maintain safety [18-20].

### Mucus mobilization in high-risk individuals

For patients at increased risk for complications, such as those requiring HFNC, delivery of 37°, 100% RH may help improvement of mucus clearance [21]. Research conducted has shown that individuals with open tracheostomies experience mucus airway drying [22]. 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. As referenced, a population known to be particularly susceptible to airway drying are those with open tracheostomy, similar to the everyday occurrence of mouth breathing during sleep, a nearly universal behavior in older populations. Furthermore, use of hypertonic saline via nebulizer may also assist in mobilization [22]. Finally, mucolytics such as Guaifenesin, nebulized N-acetyl cysteine (Mucomyst) and L Dornase are proven medications which have been shown to mobilize the mucus layer in individuals [21].

### 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 mind “get the junk out” 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, reduced involuntary cough and improved sleep should all 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.
- 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.
- Nasal washing devices, such as Navage Nasal Care [24], offer a safe means of clearing excess nasal mucus
- **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!
- Importance of wearing a mask – one study has proposed that increased humidity from mask wearing may help lessen COVID-19 severity [25–28].

### Conclusion

In conclusion, mucus hydration and mobilization are unlikely to become popular topics on the evening news or at the dinner table. For now, while we await further research, we hope healthcare providers will take the extra time to instruct and encourage patients on effective treatments. Patients will have to put aside their fixation on injections, pills, and inhalers. 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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