Appendix: Notes on Severity of the Upper Respiratory Infection in the Covid-19 Era (Interplay of Ambient Humidity and Mouth-Breathing)

Highlights Ambient humidity and mouth-breathing may be synergistic in the genesis of the upper respiratory infection (URI) after eposure.

- Mucosal barrier disruption (MBD) may be the inciting cause of the URI.
- Chronic airway inflammation and related clinical conditions from sinusitis to tonsillitis may be related to MBD.

In the development of the upper respiratory infection (URI), the the prediction of severity of disease is not only based on the degree of exposure to a pathogen (e.g Covid-19), but also on host factors beyond the status of the general immune system. In the period just prior to the pandemic, several landmark experimental reports permit a better understanding of the physical factors that may be also important in cause and effect in URI severity.

First, in 2018, Christian Guilleminault and colleagues showed in a study of nearly 7000 patients that rhinosinusitus, otitis, and antibiotic usage were highly associated with sleep-related reported mouth-breathing [1]. Second, in early 2019, a team at Yale University using experiments in a mouse model explained the link between the seasonality of URI (influenza in this case) and their tendency to be associated with cold, dry (low ambient humidity) periods: disruption of the upper respiratory mucous membrane barrier and mucociliary transport system [2].

Instead of the URI simply representing the invasion of host airway tissue by pathogens, URI may be *initially* incited by a mucosal barrier disruption (MBD) caused by the desiccation of the airway mucous membranes from a potential synergistic combination of environmental dryness (decreased relative humidity) and exposure (nocturnal mouth-breathing). This is even further supported by a study that contradicts the prevailing belief that the reason for influenza's increased prevalence in low humidity environments is due to increased viral aerosol stabilization. In the third landmark study also from 2018, a research team demonstrated that "viruses remain highly stable and infectious in aerosols across a wide range of relative humidities" [3].

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Acceptance of the conventional concept may be incomplete, especially that beyond "presence of comorbidities", little explanation is usually given for why some patients develop severe respiratory infection while others remain completely asymptomatic. One cannot help but question the comprehensiveness of this paradigm when we consider that there is so much variability in the development of disease in individuals, especially those who fail to develop disease when "exposed" and in response to treatment.

In other words, in the spectrum from the "common cold" to deaths from influenza or Covid-19, the physical breach of the airway mucosal barrier may be as important as host immune factors and pathogen load and aggressiveness in the determination of URI disease and outcome.

This alternative paradigm rests on the concept that instead of the pathogen itself being the root cause of the URI, physical/environmental forces acting on the host airway cause the mucosal barrier disruption. Then, pathogen invasion is permitted, with eventual pathogen proliferation and onset of classic disease. By deepening our understanding of the nature of these MBD forces, in addition to knowledge of pathogens and their treatment, we can consider low-cost/low-risk barrier protecting interventions.

Airway MBD may be initiated primarily by the synergistic forces of ambient humidity and exposure-induced dehydration or mechanical barometric disruption of the mucosa. Thus, the risk of URI and its outcome will be related to mucosal hydration status combined with the extent of mechanical disruption.

The hydration status of the airway mucosal barrier and its function "depends strongly on the humidity and heat in the inhaled air, the exposure time, and the health of the individual" [4]. The extent of exposure is determined by the route of breathing (nasal versus oral). Pure mouth-breathing will expose the wet mucosa to drier environmental air when compared to pure nasal breathing (more mucosal humidification) [5]. Thus, the hydration status of the mucosa may be determined primarily by the ambient/environmental humidity and the tendency for an individual to utilize primarily oral breathing. This could explain why most URIs, including influenza,and possibly Covid-19 are most apparent in the low humidity winter months where indoor heating systems dehydrate the room air. In contrast, in overly high humidity seasons/regions, barrier disruption can be due to *excess* pharyngeal water vapor, as in tropical climates, influenza peaks during high humidity [6]. In regions of very high humidity, fungal infections are endemic, not because of the prevalence of the fungus, but because essentially of the presence of excess moisture present in the airways.

Further, mechanical disruption of the mucosal barrier can be due to high levels of negative pharyngeal pressure, which builds up in the airway due to inspiration with partial upper airway obstruction. Typically, this occurs intermittently during low-tone sleep stages where due to relaxation of jaw and tongue musculature (that normally counter the effects of gravitational forces) the mouth opens, releasing the tongue into the airway and causing obstruction (aka sleep disordered breathing

[SDB] or obstructive sleep apnea [OSA]) and generating negative pressure build-up in the airway [7]. This negative pressure stretches the mucosa intra-luminally, creating focal micro-traumas upon the mucosa and resulting in the typical inflammatory response found in tonsillar, adenoid, and uvular specimen [8]. In addition, exacerbation of the disease in the upper airways can cause a build-up of negative pressure in the lower airways and alveoli, causing alveolar "stress" with eventual alveolar collapse and clinical scenario of severe acute respiratory distress. These focal areas of negative pressure–induced inflammation, if also undergoing desiccation from low ambient humidity, can become the breach-point for MBD [9].

Temporally, after pathogen exposure, the acute onset of any of these conditions (i.e., winter humidity or temporary predisposition to mouth-breathing) could induce an acute URI, while chronic exacerbations of these conditions (i.e., long-term diminished tone in the setting of elevated BMI resulting in increased OSA/SDB severity with long-term mouth-breathing) can result in chronic, or severe symptoms. An acute flu-like systemic illness could result if the barrier-breach lacks a regionally built-up immune response (like Waldeyer's ring) while systemic illness can be limited by the build-up of chronic regional immune response from chronic exposure.

Anatomic location of the MBD can be predicted as well using the "tube law" of collapsible pipes. Negative pressure build-up in the airway maximally exerts its effects on collapsing the soft mucosal sidewalls in an inward fashion at a location *just distal* from the *inspiratory* obstruction. Thus, with septal deviation or nostril narrowing, sinus mucosal in-drawing will manifest, while with nocturnal palatal collapse, the mucosal in-stretching will occur in the pharynx. More downstream obstruction, with tongue collapse in more severe sleep apnea patients (i.e, with elevated BMI), will mount excess negative pressure in the lower airways, making this area prone to MBD.

In summary, MBD may be due to the interplay of humidity-induced mucosal dehydration and mechanical damage due to negative pressure build-up in the airway during sleep from mouth-breathing/OSA/SDB. The anatomic location and temporality of URI may depend on the acuity of onset of these forces and location of maximal airway collapse, respectively.

In addition to exposure reduction strategies like social distancing, etc, patients can be redirected to attempt mucosal barrier restoration using manipulation of environmental humidity (e.g., check and adjust room humidity to 40–60%) as well as encouraging mechanical techniques to reduce mouth-breathing via mouth-closure combined with nasal dilation and OSA treatment, but more evidence is required to confirm these findings. Putting these concepts together, a severity index for respiratory infections, where the probability of severe disease is calculated for individuals or populations could be roughly equivalent to: Severity Index = Exposure (number of human contacts) × Airway Tone (Age × BMI) × Inhaled toxin exposure (pack years)/outdoor temperature as a surrogate for indoor humidity.

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