

Quote of the Day!



- For good ideas and true innovation, you need human interaction, conflict, argument, debate.

Margaret Heffernan

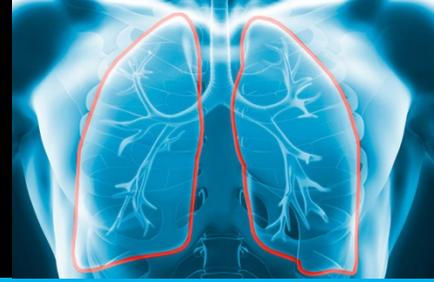
Inspired by:



Dr Alice Mary Stewart



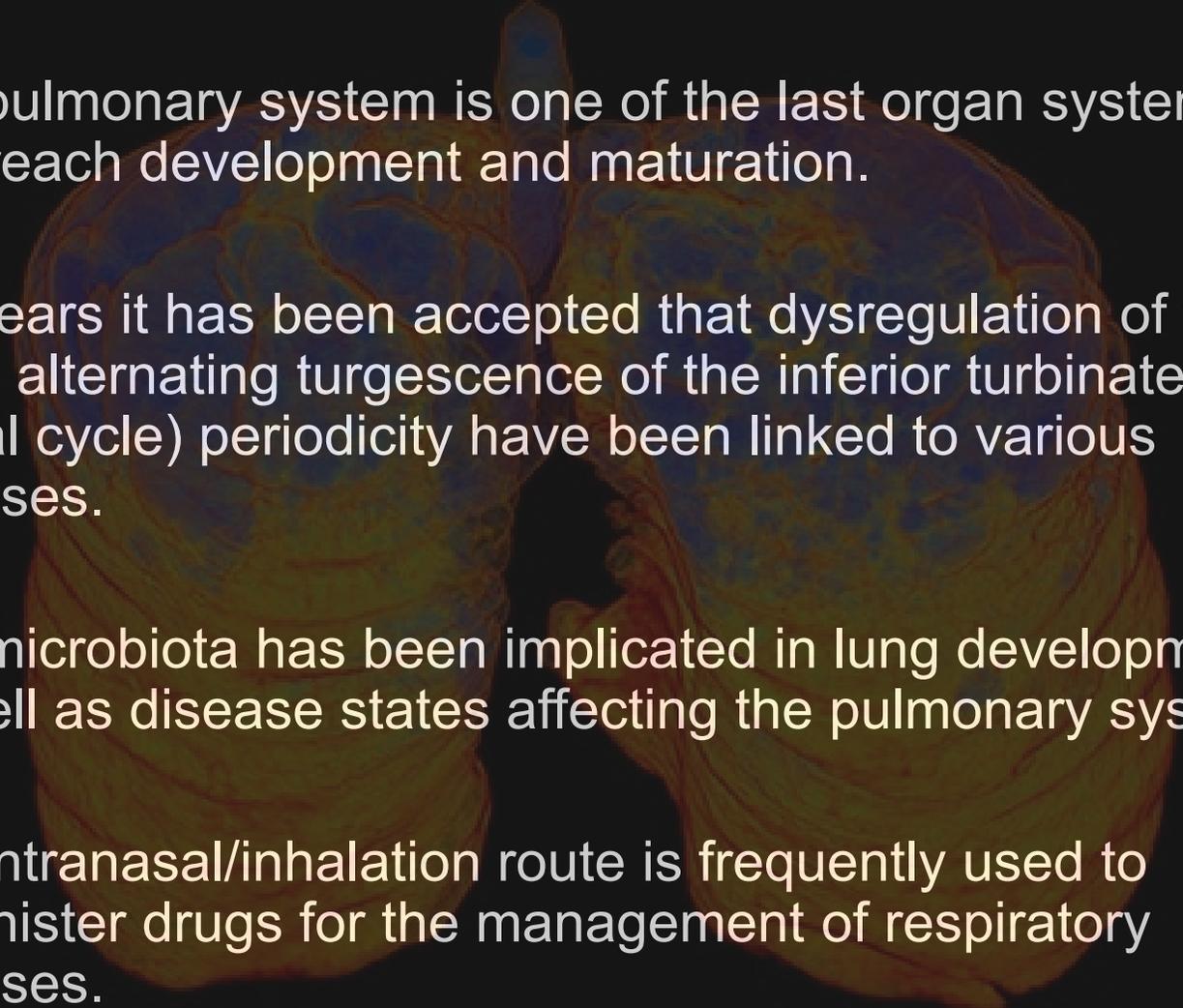
INTRANASAL/INHALATION THERAPIES & THE PULMONARY SYSTEM



- **Background Health Problem**
- **Research Agenda**
 - **Goals & Objectives**
 - *Rationale*
 - **Candidate Therapeutic Agents**
- **Evidence (Line of Studies)**
 - **Scientific Roadmap “from molecules to the community”**
 - **Basic, Translational, Applied, Clinical**
- **Conclusions**

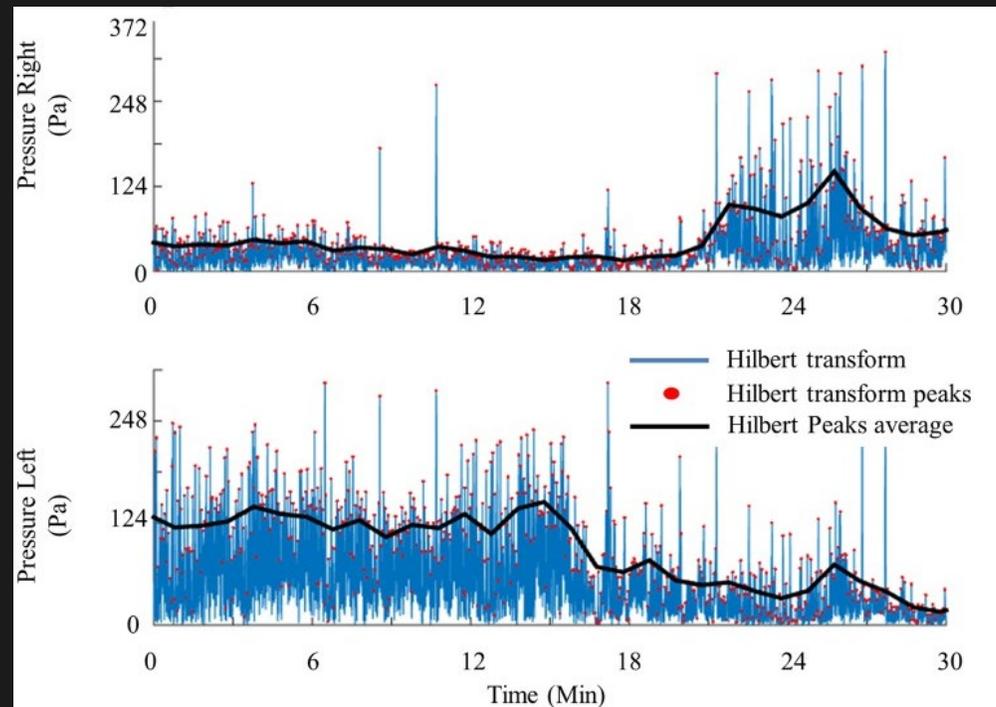


BACKGROUND

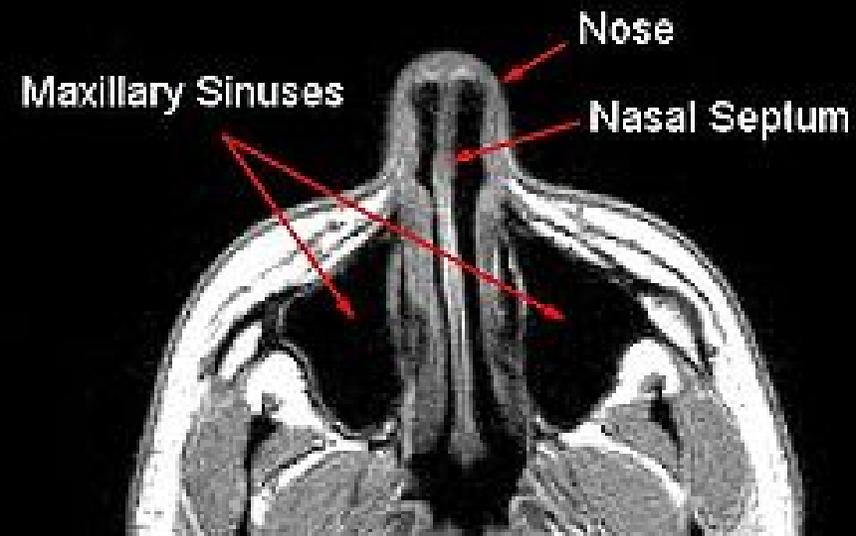
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- The pulmonary system is one of the last organ systems to fully reach development and maturation.
 - For years it has been accepted that dysregulation of the nasal alternating turgescence of the inferior turbinates (nasal cycle) periodicity have been linked to various diseases.
 - The microbiota has been implicated in lung development as well as disease states affecting the pulmonary system.
 - The intranasal/inhalation route is frequently used to administer drugs for the management of respiratory diseases.

Nasal Cycle

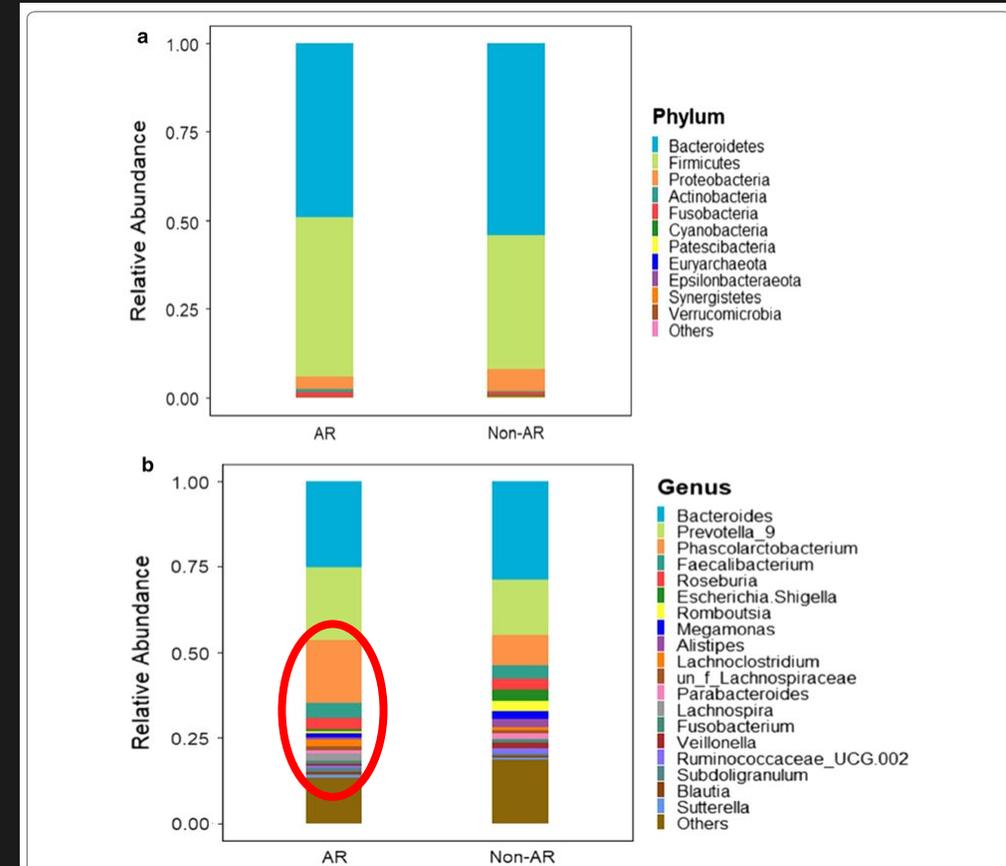
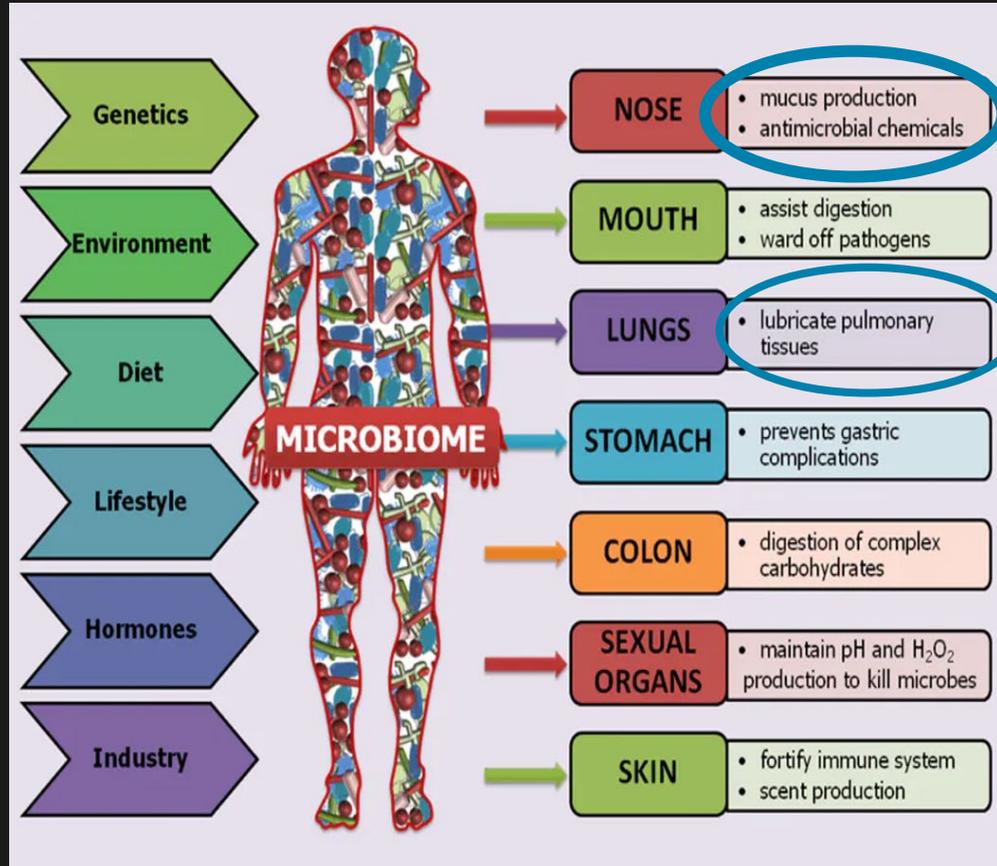
- Nasal airflow is greater **in one nostril than in the other**, and the greater airflow nostril shifts between left and right over time
- **Asymmetry in blood flow** leading to engorgement of erectile tissue in the anterior part of the nasal septum and inferior turbinate of one nostril over the other.
- Contributes **NO production** and biological functions
- Involved in **protection** against respiratory infection and allergies.



Adapted: [Kahana-Zweig et al. PLoS One. 2016; 11\(10\): e0162918](#)

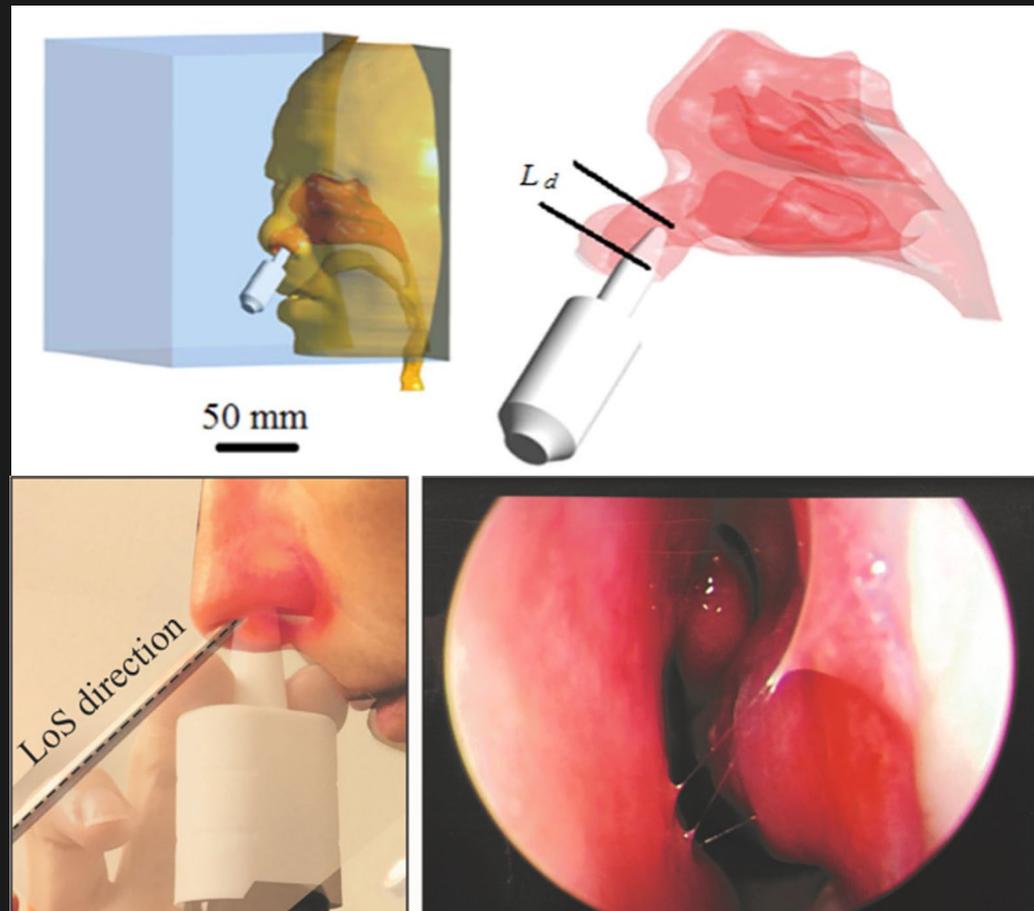


The Microbiome: The 12th Organ System?



Nasal and Inhalation Delivery

- **Rapid alleviation** and/or prevention of airway inflammation and constriction
- High nasal and pulmonary **drug concentrations** can be achieved by directly delivering the drug
- **Low systemic concentrations** and ultimately reducing the risk of side effects

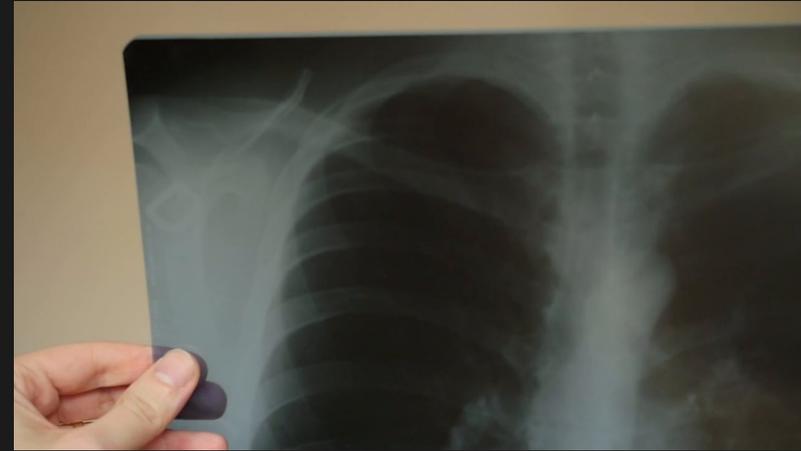


HEALTH PROBLEM

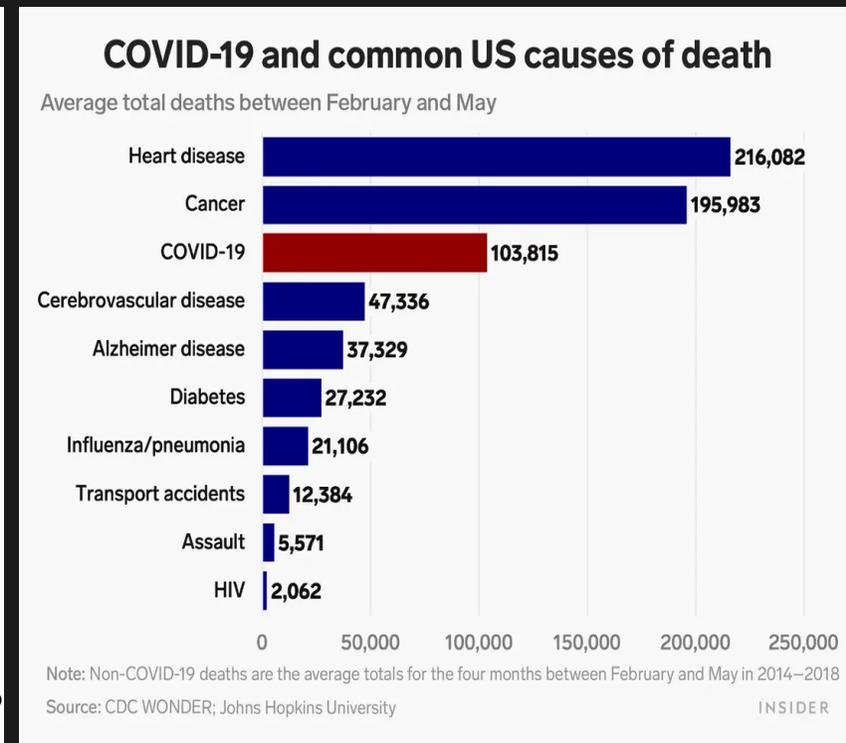
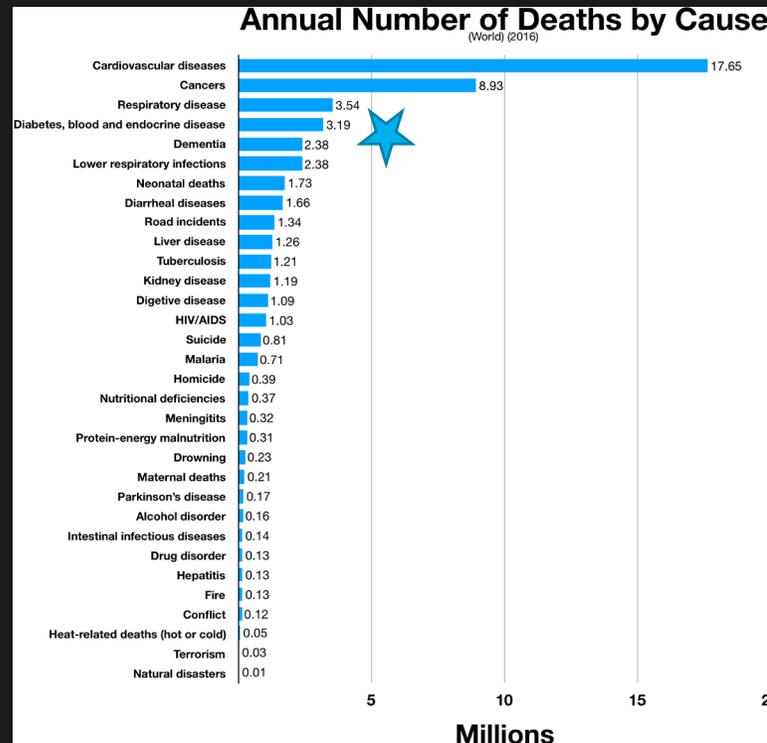
- An estimated 65 million people have moderate to severe **chronic obstructive pulmonary disease (COPD)**
- About 334 million people suffer from **asthma**
- 100 million people suffer from **sleep-disordered breathing**
- The prevalence of allergic rhinitis in the **United States** ranges from 3% to 19%, and 30 to 60 million people are affected each year.



Respiratory Disorders as Top leading causes of Death



Economic
Impact????
\$\$\$\$\$\$\$\$



OUR RESEARCH AGENDA



Purpose
&
Rationale



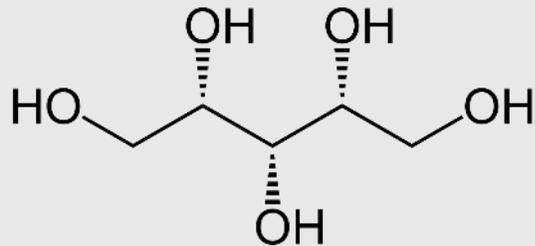
Goal, Objectives & Rationale

- Overarching Goal: To develop **effective interventions to improve the quality of life** of those suffering from pulmonary disorders.
- Objectives:
 - To unveil components with **multiple therapeutic actions and properties**.
 - To test therapies for improving pulmonary health in patients with allergic Inflammatory and infectious **pulmonary conditions**.
- Rationale: The combination of therapeutic agents delivered intranasally/inhaled capable of **reducing the main components of the allergic and inflammatory cascade as well as providing microbiome modulation** effects would provide a dual almost synergistic beneficial effect for the effective treatment of pulmonary disorders.

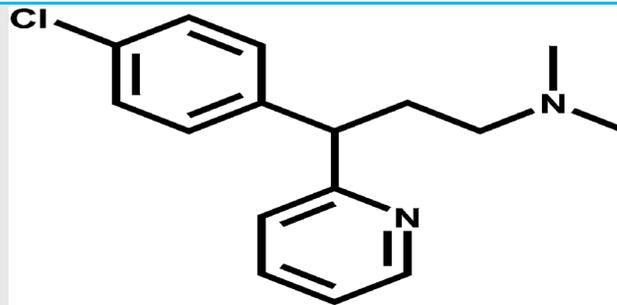


CANDIDATE AGENTS WITH MULTIPLE THERAPEUTIC CHARACTERISTICS

Xylitol



Chlorpheniramine

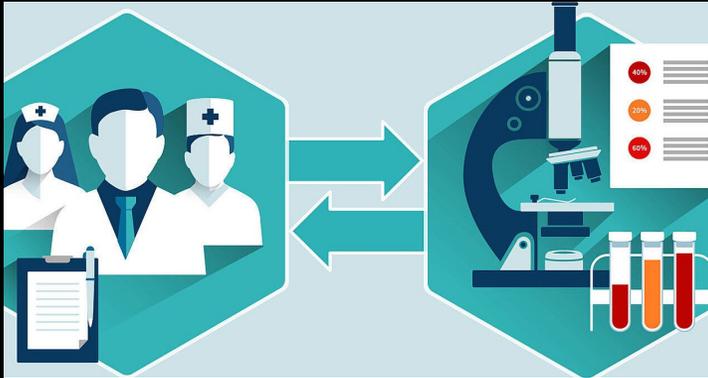


Grapefruit Seed Extract

- Virucidal
 - Fungicidal
 - Bactericidal
- 

TREATMENT

The Research Studies: From molecules to the community



Evidence-based
medicine



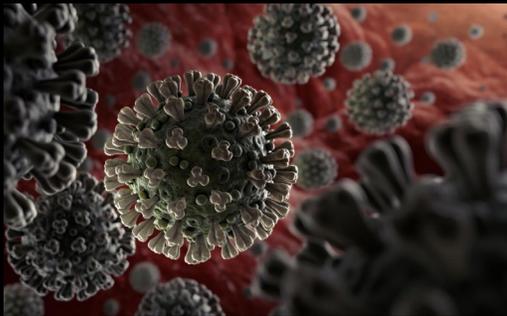
Developing intranasal/inhalation therapies for the treatment of inflammatory and infectious disorders of the pulmonary system

	Level	Example of Evidence
	Level 1	Meta-analysis of Homogenous RCTs Randomized Control Trial
	Level 2	Meta-analysis of Level 2 or Heterogenous Level 1 Evidence Prospective Comparative Study
	Level 3	Review of Level 3 Evidence Case-control Study Retrospective Cohort Study
	Level 4	Uncontrolled Cohort Studies Case Series
	Level 5	Expert Opinion Case Report Personal Observation
	Foundational Evidence	Animal Research <i>In Vitro</i> Research Ideas, Speculation



- We propose that SARS-CoV-2 can act as a trigger and substrate of an **HP-like severe immune reaction** especially in genetically vulnerable individuals in addition to those with immune senescence and dysregulation.

Is COVID-19 a **Biphasic Syndrome**?

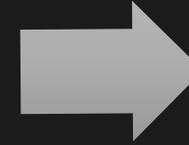


Sanchez-Gonzalez et. al Infect Chemother. 2020 Sep;52(3):e31

A Pathophysiological **Perspective** on COVID-19's Lethal Complication: From Viremia to Hypersensitivity Pneumonitis-like Immune Dysregulation

PHASE 1:Viremia: 7
Days

- ↑Viral load and allergen/antigens creating a similar environment to the pathophysiology of HP
- Check EOS and NEU/LYM baseline counts



PHASE 2:
Hypersensitivity-like
Response: From Day 8>

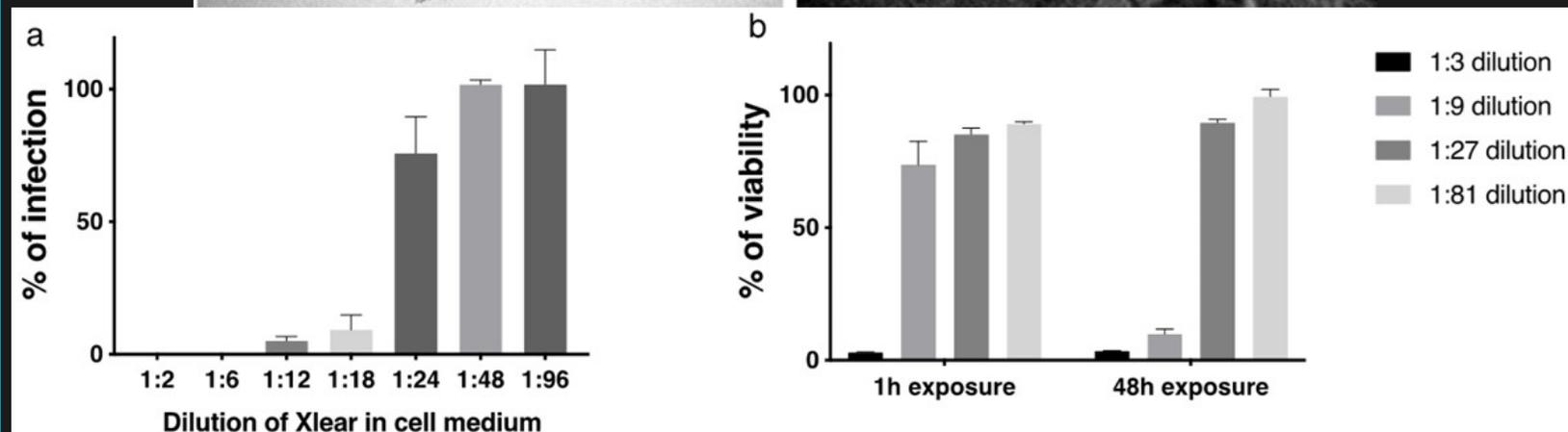
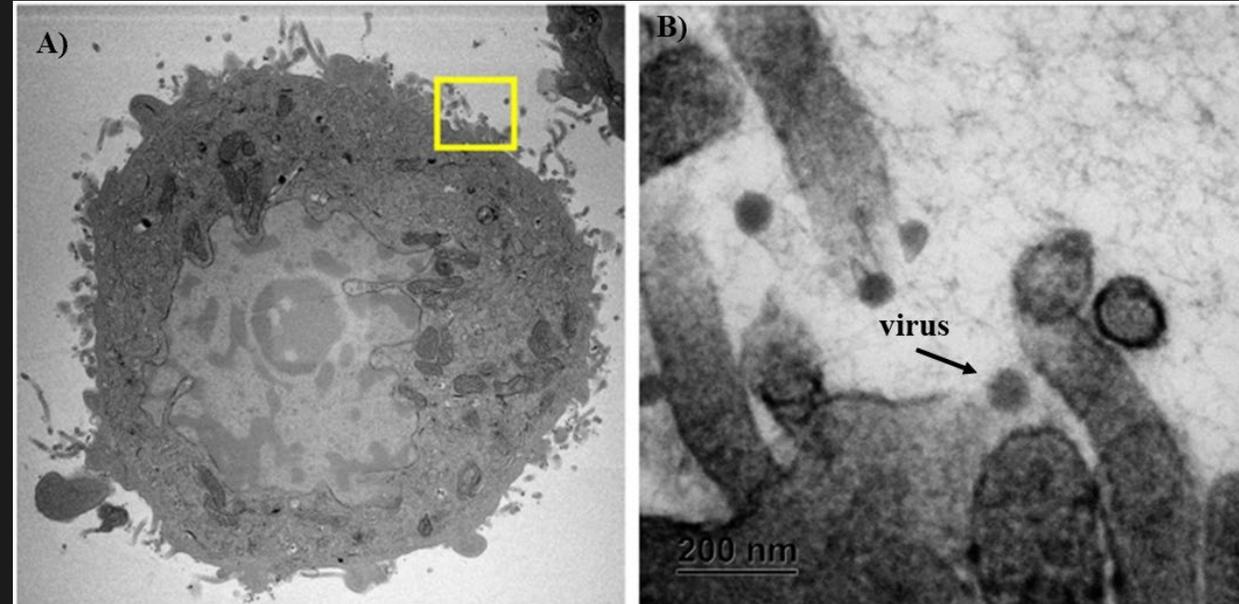
- Th2-type immunopathology with prominent EOS infiltration lungs
- ↓EOS [<0.2%] and ↑NEU/LYM [>5]
- Onset of decrease Oxygen saturation

In Vitro Analysis of the Anti-viral Potential of Nasal Spray Constituents Xylitol and Grapefruit Seed Extract against SARS-CoV-2

- To evaluate the *in vitro* virucidal effects of a solution combining **xylitol** and **GSE** in a nasal spray formulation known as **Xlear**.

Xlear displays **virucidal activity** against SARS-CoV-2 as well as the **ability to block viral entry** into the cells.

GSE significantly reduces the viral load while **xylitol** prevents the virus attachment to the core protein on the cell membrane.



Ferrer et al. *Virus Research* (under review)

- The genome sequence of COVID-19 opened the opportunity for multiple in vitro and clinical trials, but we still do not have a clear path to treatment.

Chlorpheniramine maleate (CPM) is a safe and effective antihistamine with potent antiviral activity against various strains of influenza A/B, thus suggesting that CPM has broad antiviral activity.

Nasal spray composition with CPM at 0.4%: 3.6 mg/mL.

In Vitro Virucidal Effect of Intranasally Delivered Chlorpheniramine Maleate Compound Against SARS-CoV-2

	Concentration	Incubation	Virus Titer ^a	LRV ^b
Nasal spray	90%	25 minutes	1.7 ± 0.0	2.5***
Ethanol	67.5%	25 minutes	1.0 ± 0.6	3.2***
Virus control	NA	25 minutes	4.2 ± 0.4	NA

TABLE 2: Virucidal efficacy of nasal spray against SARS-CoV-2 after a 25-minute incubation with virus at 22 ± 2°C.

^aLog₁₀ CCID₅₀ of virus per 0.1 mL, average of three replicates ± standard deviation

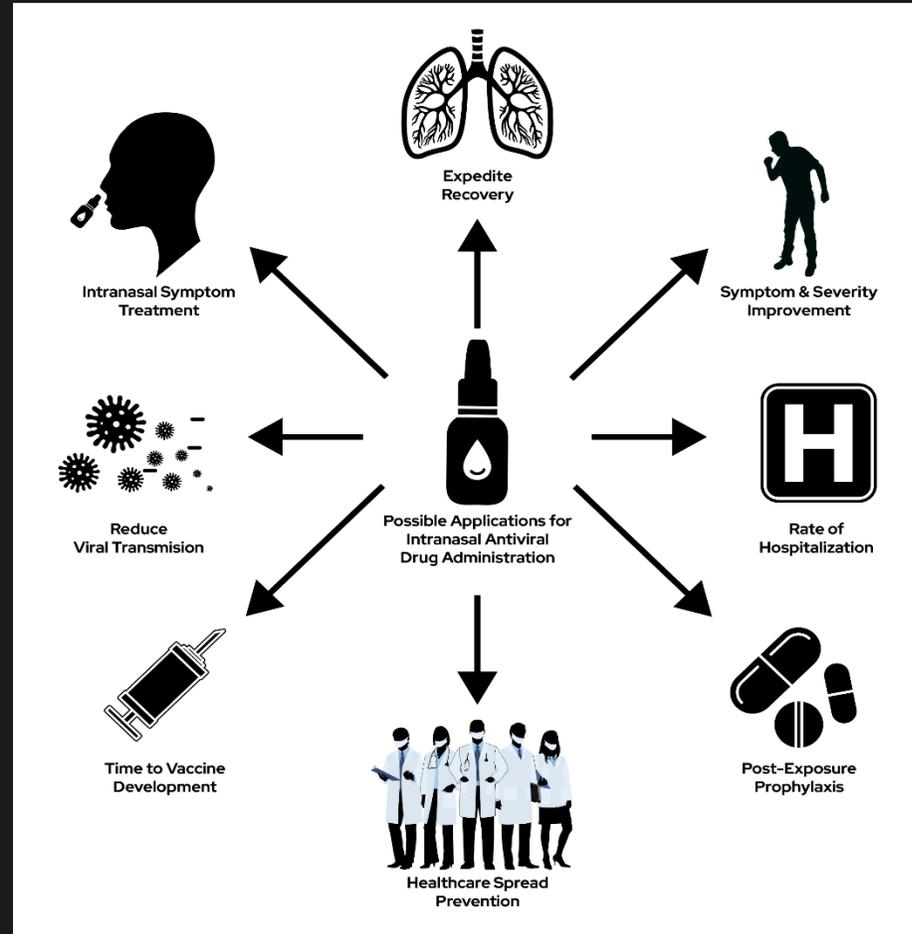
^bLRV is the reduction of virus compared with that of the virus control. For wells with undetectable virus, a value equal to the lower limit of detection was assigned for statistical analyses.

***P < 0.001 by one-way ANOVA and Dunnett's post-test compared with untreated virus control (water).

LRV, log reduction value; CCID₅₀, 50% cell culture infectious dose per mL; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ANOVA, analysis of variance

- To explore the effectiveness of using agents with **antiviral properties administered intranasally** as a novel strategy in decreasing the viral activity in the nasal pathway

Since the nasal epithelium **cells have the highest percentage of ACE2 expressing ciliate cells** in the proximal airways, it is *plausible* to suggest that the addition of **nasal disinfection** practices including using nasal sprays might be optimal candidates for providing effective preventive and **therapeutic modalities against COVID-19**.



Intranasal therapy and COVID-19: A comprehensive literature review

Go et al., J Allergy Infect Dis 2021; 2(1):9-16.

Effective Nasal Disinfection as an Overlooked Strategy in Our Fight against COVID-19

Ferrer & Sanchez-Gonzalez. Ear, Nose & Throat Journal (in press)

- Computational flow dynamics modeling to compare and contrast the conventional narrow-angle (NA) Vs a new **open-angle swirling effect (OSE)** atomizer.

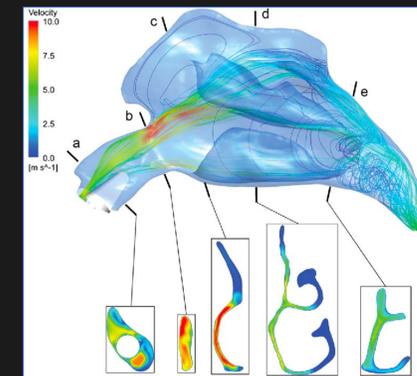
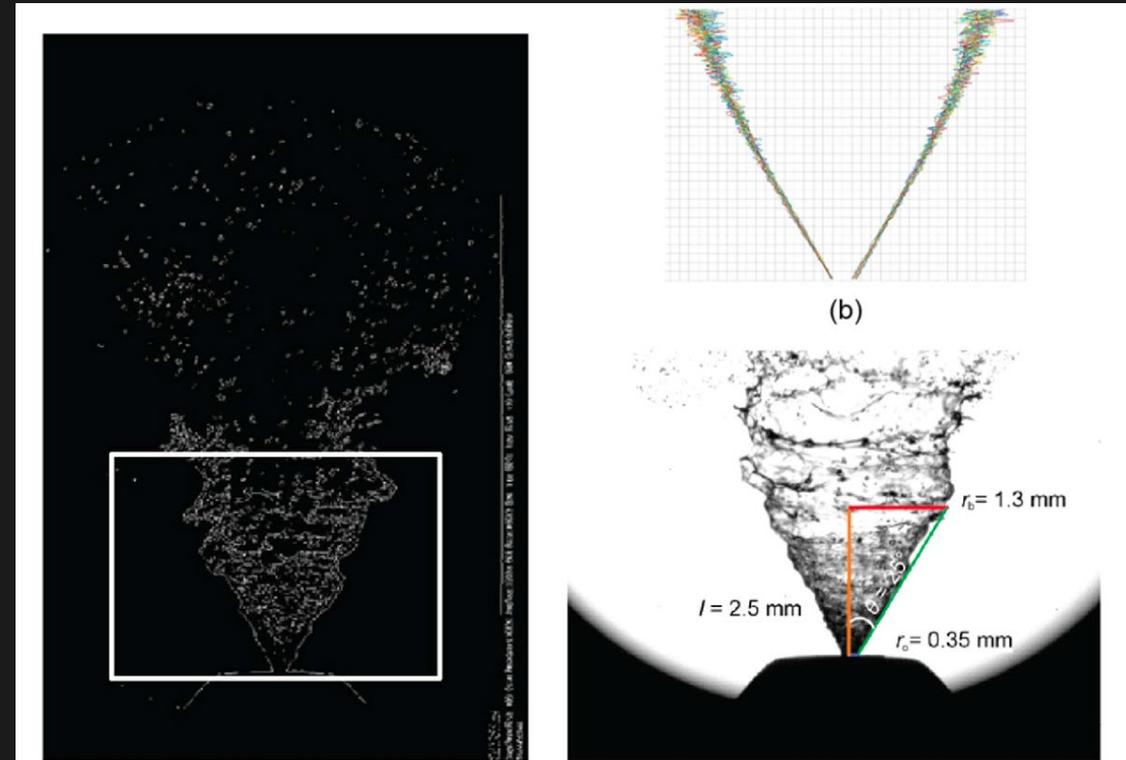
The goal for the new atomizer was to **generate a swirling effect**.

The novel atomizer reached maximum delivery doses between 3 - 7 cm, thus generating **less pressure against the mucosa**.

Gentler and more comfortable for patients.

Khawaja et. al submitted Drug Delivery and Translational Research

Development and Patient Experience Evaluation of a Gentle Atomizer for Nasal Drug Delivery



Potential Role of Xylitol Plus Grapefruit Seed Extract Nasal Spray Solution in COVID-19: Case Series

Go et al., *Cureus*. 2020 Nov 3;12(11):e11315

Chlorpheniramine Maleate Nasal Spray In COVID-19 Patients: Case Series

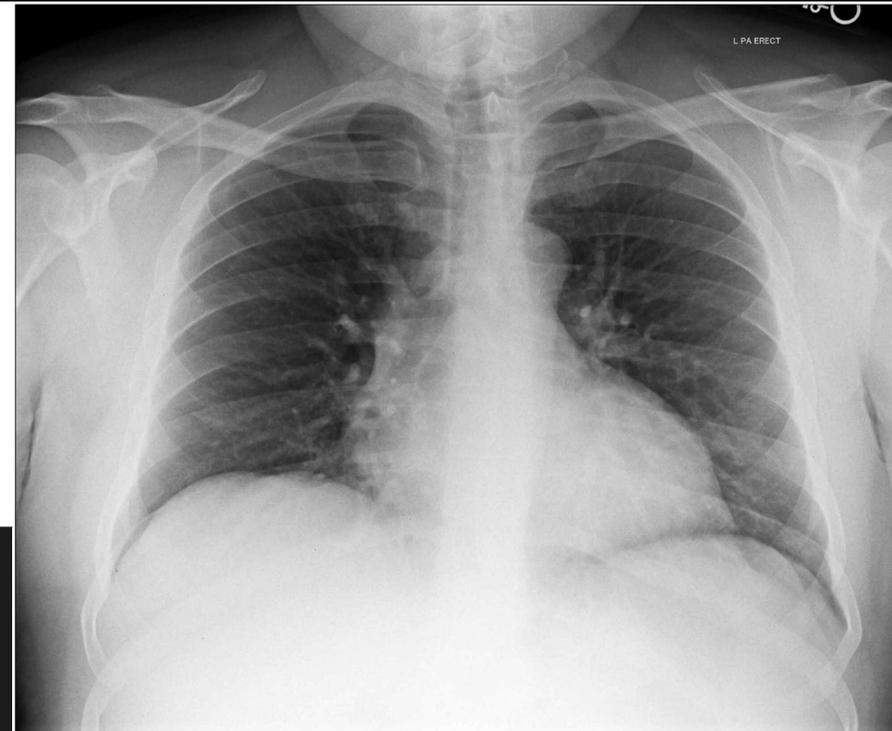
Torres et al. , *J Clin Exp Pharmacol*. 10:275. doi: 10.35248/2161-1459.21.10.275

- To explore the effectiveness of using agents with antiviral properties administered intranasally as a novel strategy in decreasing the viral activity in the nasal pathway

These case series (N=7), we conclude that CPM and Xlear nasal sprays may be a potential adjunct treatment option in patients with mild to moderate COVID-19 symptoms.

Negativization (4-7 days)

No safety issues were encountered during treatment.



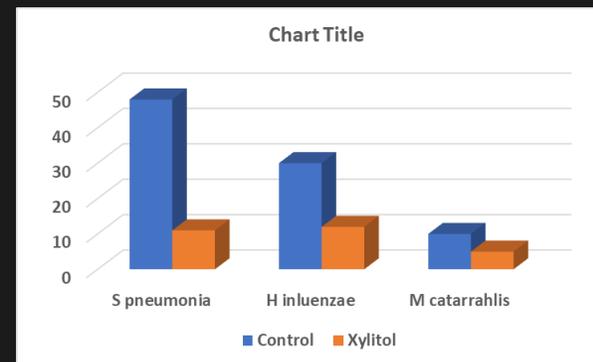
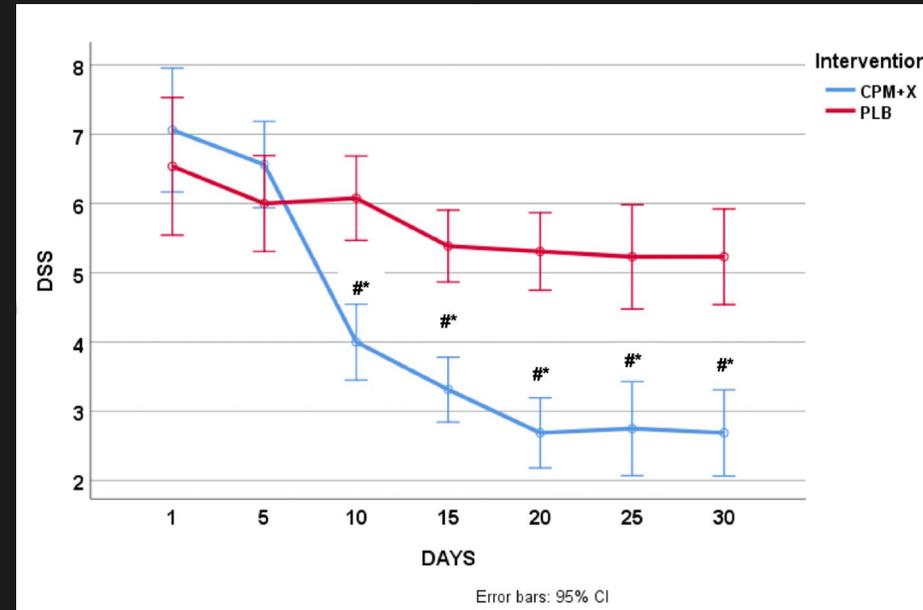
- Recent studies seem to suggest that the allergic inflammatory processes in AR may be induced by the interaction between an allergen (trigger) and the nasal microbiome (substrate).

Agents with **antihistaminic and microbiome modulating** characteristics that can be administered intranasally, namely, intranasal (CPM) and xylitol (X).

(N=29F=8)

~100 µL of the solution containing 1.25 mg CPM per nostril twice a day

A Randomized Control Pilot Trial to Test the Efficacy of Intranasal Chlorpheniramine Maleate with Xylitol for the Treatment of Allergic Rhinitis (AR)



	Level	Example of Evidence
Higher	Level 1	Meta-analysis of Homogenous RCTs Randomized Control Trial

- Notion that COVID-19 is a **biphasic clinical syndrome** with a viremia followed by hypersensitivity-like responses owing to immune dysregulation

Our group has identified a candidate drug that may be administered intranasally with both **antiviral and antiallergic/inflammatory properties**, chlorpheniramine maleate (CPM) n=26

Such an agent might work as a **“double-edged sword”** in controlling the viremia phase as well as the blunting of the hypersensitivity-like responses associated with COVID-19.

Efficacy of Chlorpheniramine Maleate Nasal Spray for the Treatment of COVID-19: A Short Report

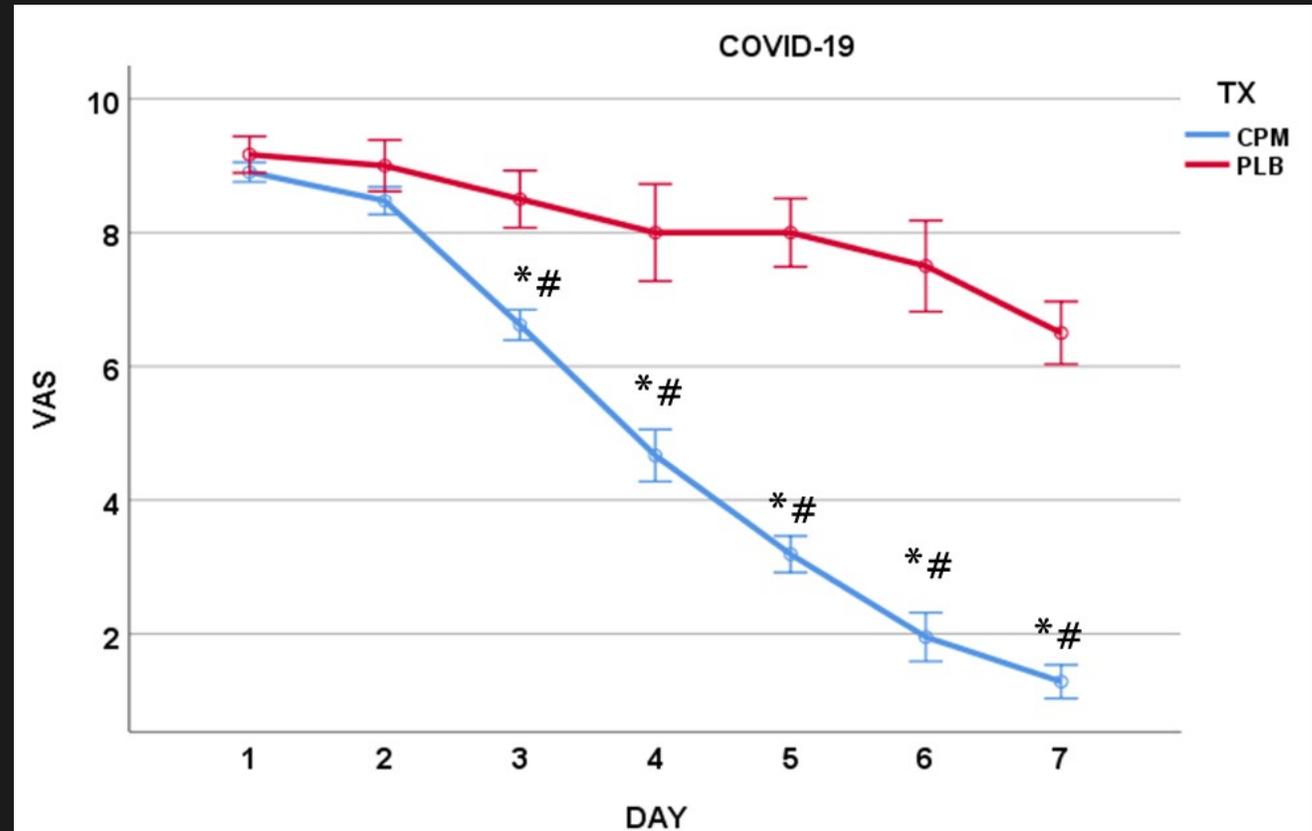


Figure 1. Data are Mean \pm 95%CI. Changes in visual analogue scale (VAS) in response to Chlorpheniramine Maleate (CPM) and placebo. # P<0.01 vs PLB. * P<0.001 vs. Day 1.

- A nasal spray formulation containing Xylitol with grapefruit seed extract (GSE) (Xlear®) has not been tested as a means to prevent AOM in children.

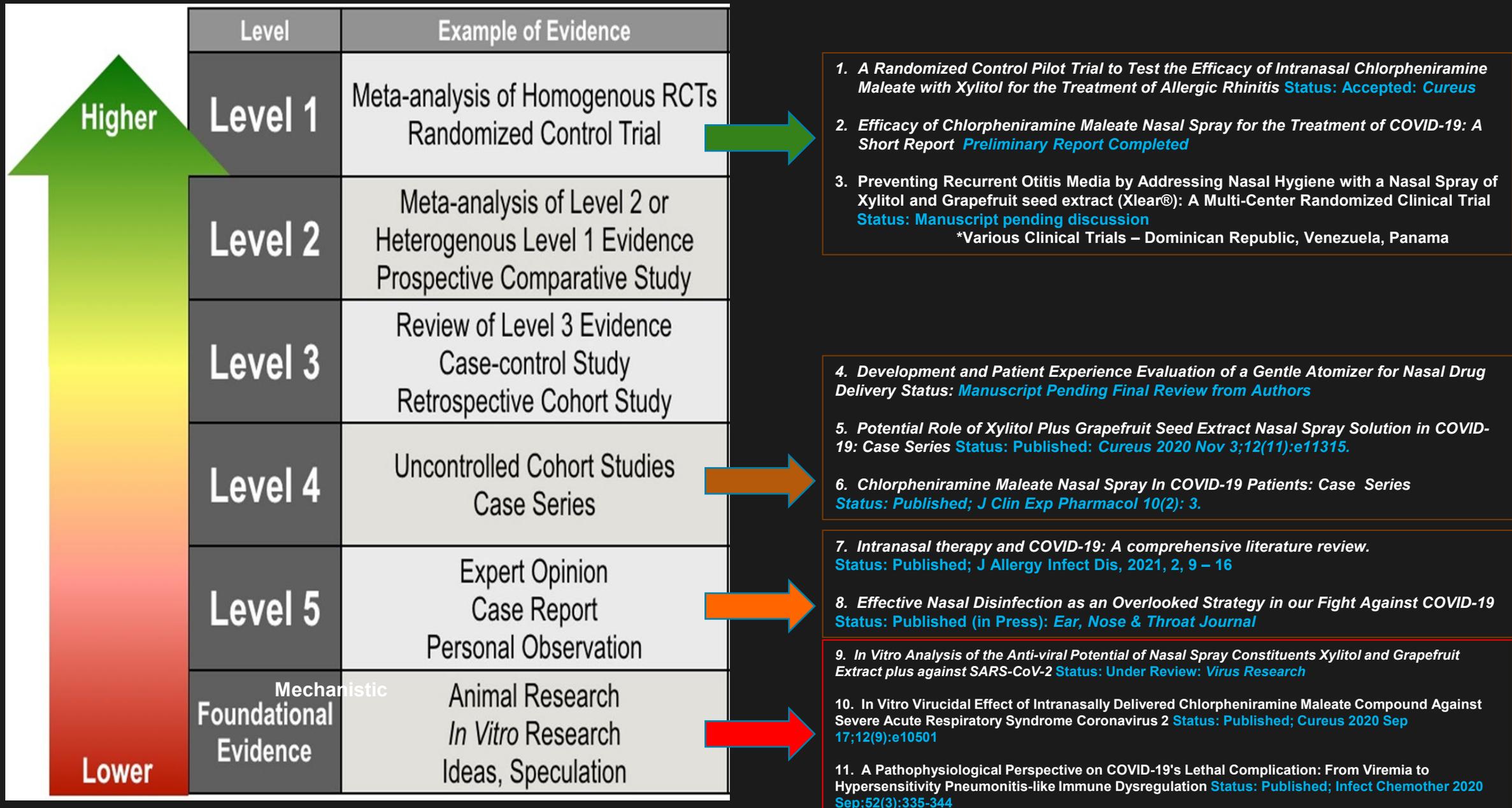
We observed 31 recurrences of AOM in a group of 80 treated with a solution (39%) vs 90% for AOM episode in the control group. For the reason of AOM episode, there were 9 cases (12% of patients) treated by antibiotics in the Xlear group compared to 35.1% in the control group. There was 2.3 times lower frequency of AOM in the Xlear group compared to the control.

Preventing *Recurrent Otitis Media (AOM)* by Addressing Nasal Hygiene with a Nasal Spray of Xylitol and Grapefruit seed extract (Xlear®): A Multi-Center Randomized Clinical Trial

Bacterial Strain	Xlear® Before		Xlear® After		Control Before		Control After	
	nose	throat	nose	throat	nose	throat	nose	throat
<i>Str. pneumoniae</i>	10	9	0	0	9	6	0	0
<i>S. aureus</i>	5	0	2	0	5	2	12	8
<i>Haemophilus spp.</i>	2	6	0	1	2	4	2	2
<i>H. influenzae</i>	1	2	0	0	4	1	3	0
<i>Str. Betahemolyt.</i>	2	0	0	0	2	3	0	0
<i>S. Milleri</i>	2	0	0	0	1	0	0	0
<i>E. coli</i>	0	1	0	0	0	0	0	0
<i>Moraxella cat.</i>	0	0	1	0	2	0	2	0
<i>Branhamella cat.</i>	0	0	0	1	0	0	0	3
<i>Total</i>	22	18	3	2	25	16	19	13

Table 1. Effects of Xlear and Control on Bacterial colonization of nose and throat by microbial examination (3 months).

DEVELOPING INTRANASAL/INHALATION THERAPIES FOR THE TREATMENT OF INFLAMMATORY AND INFECTIOUS DISORDERS OF THE PULMONARY SYSTEM



MAIN TAKEAWAYS

- The nasal cycle and the nasal microbiome as they relate to pulmonary health – [Broad Targets](#)
- Phases of the therapeutic pipeline in the context of pulmonary disorders – [molecules to community](#)
- Multiple advantages of the intranasal/inhalation rout – [high efficacy low side effects](#)
- Multiple properties of Xylitol, Chlorphenamine, and grapefruit seed extract – [acute chronic and disorders](#)
- Cost effectiveness of broad-spectrum therapeutic agents – [↑ accessibility](#)



ACKNOWLEDGEMENTS

- Zafar Nawaz
- Camille Celeste Go
- Krunal Pandav
- Manoj Reddy Somagutta
- Jacqueline Kaye Go
- Arian Bethencourt-Mirabal
- Kinal Bhatt
- Gustavo Ferrer
- Joselit Torres
- Camille Celeste Go
- Farah Chohan
- Genesis Camacho
- Syed Rizvi
- Nathan Jones
- Dave Moskowitz
- Priya D. Issuree
- George Yatzkan
- Troy Grogan
- Kenneth Day
- Mark L. Cannon
- Arian Bethencourt-Mirabal
- Hector Vazquez
- Uzzam Ahmed Khawaja
- Jonna B. Westover
- Valeria Cagno
- Caroline Tapparel
- Reiner Bleher
- Everyone involved!!!!



QUESTIONS??

Thank you very much!



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