Worth Its SALT?

Hypertonic Saline Revisited

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Disclosures

1. The opinions expressed in this lecture are mine alone. They do not purport to represent the opinions or views of the State University of New York at Stony Brook or any of its employees, faculty or entities including the Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine.

2. I disclose a previous relationship with Westmed, Inc. of Tucson AZ as Director of Clinical Education and responsibilities for product development, marketing and clinical education of a commercial ‘hypertonic saline for inhalation’ product plus companion aerosol delivery system and acoustic airway clearance device.

3. In the event that I mention these products by name during this presentation, I will identify the potentially commercial aspect of those references at that time.

Sodium Chloride (NaCl)
aka Salt

Sodium chloride, also known as salt, common salt, table salt or halite, is an inorganic compound with the formula NaCl. Sodium chloride is the salt most responsible for the salinity of the ocean and of the extracellular fluid of many multicellular organisms. As the major ingredient in edible salt, it is commonly used as a condiment and food preservative.
What do we know about salt?

Sodium Chloride (NaCl) exists naturally as a solid ...
Sodium Chloride (NaCl) … and as an aqueous solution

NaCl (aq) aqueous solution

Saline is simply the name given to the solution that results when salt (NaCl) is dissolved in water (H₂O).
B. TRAMS

- Contraction
- Proliferation
- Migration
- ECM remodeling
- Apoptosis
- Inflammation
- Angiogenesis
- Hypertension

\[ \text{Na}^{+} \quad \text{Cl}^{-} \quad \text{Mg}^{++} \quad \text{Ca}^{++} \quad \text{K}^{+} \]
The Kabbalah of Salt

A ring of salt will protect you.
The health benefits of salt therapy

“The negatively charged ions in salt improve our health and mood. Inhaling particles may reduce inflammation and mucus in the lungs, improving respiratory conditions such as asthma, allergies, bronchitis, sinus congestion and Chronic Obstructive Pulmonary Disease (COPD).”
https://www.organicspamagazine.com/benefits-of-salt-therapy/

“Salt therapy is a 100% natural alternative to effectively manage your symptoms from respiratory conditions such as asthma, bronchitis, COPD, emphysema, smoker’s cough and cystic fibrosis. As you breathe the dry microscopic salt particles deep into your lungs, they line the walls of your airways, helping to kill bacteria and viruses, and aiding in the clearing of mucus. This process reduces inflammation in the entire respiratory tract, allowing you to breathe easier. The salt is working as a "bronchial brush" for the airways.”
https://www.thesaltsuite.com/respiratory/

“Dry salt is super absorbent and acts like a sponge, attracting foreign substances along its path through the respiratory system. Dry salt can be imagined to behave like a toothbrush that cleans through the respiratory system, removing build-up of foreign elements that cause various respiratory ailments and conditions. Clean lungs, healthy lungs. Start Halotherapy today!”
https://www.salttherapyassociation.org/benefits-of-salt-therapy

“Salt therapy is a widespread tradition which philosophers and healers have recommended for hundreds of years. The origin of Dry salt therapy can be traced back to cave therapy, which regularly visit salt caves have found to exhibit fewer respiratory conditions as a direct result of inhaling the salty air within.”
My kind of salt ... "Wasting away again in Margaritaville, looking for my lost shaker of salt ... "
Everyone Knows What Mucus Is
• Usually, it is thin, clear and only slightly viscous.
• But when it gets infected, it has a bad-ass attitude.

Sputum* is a different story altogether

* or phlegm, as Dr. Bruce Rubin calls it
The Mucociliary “Escalator”

Pseudostratified, ciliated, columnar epithelium

Healthy airway epithelium

In the healthy airway, the mucus layer and the perciary layer (PCL) of the airway surface liquid (ASL) are normal thickness and consistency. Electrolyte (Na⁺ and Cl⁻) exchange is normal allowing equilibrium of water in order to maintain proper viscosity of airway secretions.

Normal Airway Mucus

Composition

- 95% water
  - Need for water intake to replenish
  - Mucus doesn’t easily absorb water once created

- 1% lipids
- Less than 0.3% DNA

Mucus

Glycoprotein

- Large (macro) molecules
- Strands of polypeptides (protein) that comprise the basic structure of the molecule
  - Strings of amino acids
- Carbohydrate side chains
- Chemical bonds “hold” mucus together
  - Intramolecular: Dipeptide links
    - Connects amino acids
  - Intermolecular: Disulfide & Hydrogen bonds
    - Connects adjacent macromolecules
Hydrogen Bond

Disulfide Bond

Physical Bonds

Calcium Bonds

DNA

DNA

CF Mucus is Different

Healthy mucus

CF sputum

Healthy airway epithelium

In the CF airway, due to the fundamental defect in Cl⁻ transfer, water is maintained in the epithelium and does not adequately hydrate the ASL. As a result, the mucus layer enlarges and becomes more viscous while the PCL shrinks due to loss of water. The cilia do not function adequately and mucociliary clearance diminishes leading to inspissated and infected secretions and a viscous cycle.

Pulmonary Drug Delivery aka Aerosol Therapy aka Inhalation Therapy

These 3 synonymous terms all relate to the procedure of administering medications, in the form of breathable aerosols, into the upper and lower airways of the respiratory tract in order to either provide or elicit a therapeutic effect via topical application of a specific substance.

**Historical factoid:** Forrest M. Bird, ScD MD coined the term “Topical Pulmonary Chemotherapy” around 1964 to signify the delivery of wetting agents and racemic epinephrine to the airways.

Classes of Inhaled Drugs
Mucoactive

*Mucoactive* is the general term applied to medications used to enhance secretion removal or reduce hypersecretion.

- Expectorants
- Mucolytics
- Mucokinetics
- Mucoregulatory

Mucoactives specifically for Inhalation Therapy

- n-acetylcysteine
- recombinant human DNase
- ✓ hypertonic saline
- Mucomyst®
- Pulmozyme®
- HyperSal®
- Nebusal™
- PulmoSal™
n-acetylcysteine

[ not used much anymore ]

Mucomyst® 10% & 20% Inhalation Solution, 4 mL
(may also be used orally for other purposes)

dornase alpha
(recombinant human DNase)

[ specific for CF sputum ]

Pulmozyme® Inhalation Solution
2.5 mg / 2.5 mL
hypertonic saline

PulmoSal 7% (pH+)
60 each, 4-mL unit dose vials per package

Commercial Disclosure: I had a previous relationship with the marketing of this product.
We already defined saline

What does *hypertonic* mean?

The normal, "isotonic" concentration of NaCl in much of the human body fluids is ~0.9\%.

![Isotonic NaCl concentration in the human body](chart.png)
Tonicity

Isotonic (aka “normal” or “physiologic”) saline has a sodium chloride (NaCl) concentration of 0.9%. It is called physiologic because it is isotonic, i.e., it has the same salt concentration as many body fluids (e.g., tears, airway surface liquid).

would be anything less than 0.9%, and would be anything greater than 0.9%.

Tonicity is responsible for Osmosis
Tonicity is a measure of the effective osmotic pressure gradient (as defined by the water potential of the two solutions) of two solutions separated by a semipermeable membrane. In other words, tonicity is the relative concentration of solutions that determine the direction and extent of water diffusion.

Therefore, a solution, such as sodium chloride (NaCl) dissolved in water, can be said to be: isotonic, hypotonic or hypertonic, depending on the concentration of NaCl present in the solution, the NaCl concentration in the human body.

Tip! Just remember: “water goes from low to high”
This picture demonstrates the effect of tonicity on red blood cells, for example. When RBCs are immersed in a hyper tonic solution, their water is transported out of the cells by osmosis, causing them to shrink. When RBCs are immersed in a hypotonic solution, water is transported into the cells, causing them to swell and possibly burst.

- What are the indications (types of patients) for hypertonic saline inhalation therapy?
- What are the pulmonary effects of hypertonic saline?
Indications for inhalation of hypertonic saline

- The principle indications for inhalation of hypertonic saline are in patients of all ages and pediatric patients with cystic fibrosis (CF).
- Use in mucus-producing COPD, such as chronic bronchitis and bronchiectasis, may have a beneficial effect and is not as firmly established as CF, but may be beneficial in some patients.

Pulmonary effects of hypertonic saline

When inhaled into the tracheobronchial tract it is thought that hypertonic saline exerts an osmotic effect whereby it pulls fluid (with a lower NaCl concentration) from the mucosa, and into the airway underneath the mucus layer, (towards the higher concentration NaCl) thereby helping to loosen and thin the secretions.

Tip! Just remember: “water goes from low to high”
In the CF airway, due to the fundamental defect in Cl\(^-\) transfer, water is maintained in the epithelium and does not adequately hydrate the ASL. As a result, the mucus layer enlarges and becomes more viscous while the PCL shrinks due to loss of water. The cilia do not function adequately and mucociliary clearance diminishes leading to inspissated and infected secretions and a viscous cycle.


Treatment with hypertonic saline is thought to reduce mucus viscosity and aids its clearance by various mechanisms. The high salt concentration encourages osmosis of water into the ASL and thereby rehydrates the mucus and partially restores the perciliary layer allowing for easier clearance of mucus.\(^1\)

Summary from the Reeves paper


Airway Schematic

Airway

ASL = Airway Surface Liquid

Ciliated cells, etc.

Basement membrane
Isotonic Aerosol

- No osmotic gradient
- Water moves both ways
- Added NS slightly increases ASL volume

Hypotonic Aerosol, e.g. Water

- Inward osmotic gradient
- Water removed from airway
- Sub-epithelial edema likely
Hypertonic Aerosol

- Outward osmotic gradient
- Water moves to airway
- Added HS increases ASL volume even further

Bronchiolitis

Hypertonic saline or high volume normal saline for viral bronchiolitis: Mechanisms and rationale

Mandelberg Ped Pul 2010 45 36

Maintaining normal height of the PCL ensures proper fluid clearance for maintaining normal airway mucociliary clearance (MCC) so that the moving cilia of the MCC precisely contact the lower margin of the ML.

Pulbiciliary liquid = 7 um
Clinicians may administer nebulized hypertonic saline to infants and children for bronchiolitis (Evidence Quality: B; Recommendation Strength: Weak Recommendation).
HYPERTONIC SALINE

Key Action Statement 4a
Nebulized hypertonic saline should not be administered to infants with a diagnosis of bronchiolitis in the emergency department (Evidence Quality: B; Recommendation Strength: Moderate Recommendation).

Grey Area ?
Use of hypertonic saline in COPD

• Induced sputum experience lingers in the mind of pulmonologists: **use of 10% HS to induce coughing**.
• Hypertonic saline is inherently irritating to the airways due to its acidity.
  ✓ The greater the salinity, the lower the pH
  ✓ 3% may be too weak to do much good
  ✓ 7% may be more effective but may also elicit bronchospasm
Use of hypertonic saline in COPD?

Various microscopic images of Pseudomonas organisms showing rod-like shape (bacillus) and flagella for motility.
**Pseudomonas aeruginosa**

*Genus:* Pseudomonas; *species:* aeruginosa

- *Pseudomonas aeruginosa* is a common Gram-negative rod-shaped bacterium that can cause disease in plants and animals, including humans. A species of considerable medical importance, *P. aeruginosa* is a prototypical "multi drug resistant (MDR) pathogen" that is recognised for its ubiquity, its intrinsically advanced antibiotic resistance mechanisms, and its association with serious illnesses - especially nosocomial infections such as ventilator-associated pneumonia and various sepsis syndromes.

- The organism is considered opportunistic insofar as serious infection is often superimposed upon acute or chronic morbidity - most notably cystic fibrosis and traumatic burns - or found in immunocompromised individuals.

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**Age-Prevalence of Psa in CF**

By age 10, *Psa* starts to proliferate. By the late teens, it becomes the dominant pathogen in cystic fibrosis patients.
**PulmoSal™ 7% (pH+)**

- Hypertonic Saline
- 7% NaCl solution
- Buffered with sodium bicarbonate (NaHCO₃⁻)
- NaHCO₃⁻ buffers H⁺ ions
- Therefore, pH = 7.40

*Commercial Disclosure: I had a previous relationship with the marketing of this product.*

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**pH-DEPENDENT DIFFERENTIAL PSEUDOMONAS AERUGINOSA KILLING IN CF SPUTUM INCUBATED IN HYPERTONIC SALINE SOLUTIONS**

Burns *in vitro* study

- “These data show approximately 5 log decrease in bacterial density in the pH 7.4 solution compared with approximately 2 log decrease in the pH 5.86 and pH 6.60 solutions at 24 hours. The density difference between solutions is even more dramatic at 8 and 12 hours.

- Given the dosing frequency of 7% HS in CF, these findings suggest that the use of physiologic pH solution could have a marked impact on bacterial density in CF sputum.”

*Jane L. Burns, Adam Griffith, Seattle Children’s Hospital and University of Washington, Seattle, WA*

*2014 NACFC Pediatric Pulmonary supplement page 351.*
Summary

- HS has been in use for 50+ years; it has gone in and out of favor.
- EBM has not been particularly kind to HS.
- But many clinicians and patients believe it works.
- **It is a staple of mucoactive inhalation therapy in CF.**
- Newfound attention is being given to the ASL in CF and factors that influence its function.
- ASL pH is a new area for research and HS will likely be part of future investigation in this area.
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