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Review

The Role of Seawater and Saline Solutions in Treatment of Respiratory Conditions

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Abstract:

The history of saline nasal irrigation (SNI) is indeed a long one, beginning from the ancient Ayurvedic practices and starting to gain a foothold in the west at the beginning of 20th century. Today, there is a growing number of papers covering effects of SNI from in vitro studies to randomized clinical trials and literature overviews. Based on the recommendations of most of the European and American professional associations, seawater, alone or in combination with other preparations, has its place in treatment of numerous conditions of the upper respiratory tract (URT), primarily in chronic (rhino)sinusitis, allergic rhinitis, acute URT infections and postoperative recovery. Additionally, taking into account its multiple mechanisms of action and mounting evidence from recent studies, locally applied seawater preparations may have an important role in prevention of viral and bacterial infections of the URT. Therefore, in this review we discuss results published in the past years focused on the seawater preparations and their use in clinical and everyday conditions, since such products are superior to saline, have an excellent safety profile and are recommended by most professional associations in the field of otorhinolaryngology.

Keywords: seawater; seawater preparation; Aqua Maris; nasal irrigation; upper respiratory track; otorhinolaryngology

1. Introduction

The use of water for prophylactic or therapeutic purposes, mostly in respiratory system, has been known since ancient times. In Yogic practices, different nasal cleansing techniques are used as part of a wider range of body cleansing procedures. Vedic texts describe several techniques called "neti" [1,2] with "jala neti" [3,4] corresponding to today's concept of nasal cavity irrigation. In the neti techniques, copperware was used for irrigation (to prevent contamination of the solution), the solution was heated to body temperature and an exact salt concentration in the preparation of solution was specified. This salt content and, consequently, the osmolality of the solution remained one of the most important parameters in nasal irrigation to the present day.

The osmolality of the commercial compositions of NaCl solution ranges from physiological 0.9% to hypertonic solutions with an osmolality of 3% [2]. Solutions with higher

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osmolality tend to induce side effects. The osmolality of the solution results not only from NaCl content but also from the other ions contained therein. Besides having effect on osmolality, the ions also show a number of effects on the biology and function of cells and tissues. This is especially important because many commercially available formulations, primarily these based on seawater, contain a number of ions other than Na^+ and Cl^- and differ significantly from the galenic saline. In this review, the following parameters of these solutions will be discussed:

Composition of solution in context of differences between saline and solutions based on seawater,

Mechanism of action in nasal cavity and elsewhere,

Safety and efficacy of use in different indications.

2. Composition of saline/seawater preparations

Unlike saline, which consists of NaCl dissolved in distilled water, in seawater there are four categories of constituents or solutes: major constituents, minor constituents, trace elements and gases. Average salinity of undiluted seawater is approximately 3.5% or 35 ppt (parts per thousand). Ninety-nine percent of seawater salinity is due to 6 major constituents: Cl^-, Na^+, SO_4^{2-}, Mg^{2+}, Ca^{2+} and K^+. Salinity is relatively uniform, with range of variation of 33-37 ppt in open ocean water, 37-38 in smaller bodies of seawater such as the Adriatic Sea to as much as 240 ppt in the Dead Sea. This is why the source of water in seawater products is such an important factor.

One of the fundamental laws in oceanography, the Forchhammer principle or the principle of constant proportions, states that the relative proportions of the major constituents of seawater are constant, regardless of different salinities in different sea-water samples. Cl^- accounts for 55% of the ions, followed by Na^+ (30.6%), SO_4^{2-} (7.7%) and Mg^{2+} (4%). Major constituents are also considered to be conservative, i.e., chemically non-reactive and thus stable in oceans and seas over the long periods of time. Besides major constituents, measured in ppt, seawater also contains a number of minor constituents (measured in ppm – parts per million) and trace elements, measured in ppb – parts per billion. However, the principles that apply to the major elements do not apply to the minor and trace elements. This means that many of these elements are biologically or chemically reactive and that their concentration can be dependent on biological activity and other factors, exhibiting significant local differences. Major constituents of seawater with salinity of 35 ppt at the temperature of 25°C are shown in the Table 1.

Table 1. Major constituents of seawater (mg/dm^3)

Constituent	Dittmar (1940)[5]	Cox (1966)[6]	Riley (1967)[7]	Millero (1996)[8]	Štanfel (2006)[9]
Cl^-	19805	-	-	19805	19763
Na^+	11015	11013	11037	11035	**12117**
SO_4^{2-}	2764	-	2776	2764	2707
Mg^{2+}	1327	1327	1322	1314	**1417**
Ca^{2+}	418	422	422	422	**474**
K^+	397	408	408	408	**443**
Br^-	67	-	69	69	63

From Table 1 is evident that the cations (sodium, potassium, calcium and magnesium) determined in Adriatic Sea (Kvarner bay) by the ion-chromatography method are higher than cations obtained by various authors mentioned in the Table 1.

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Table 2. Minor constituents of seawater[8]

Constituent	g/kg	AW	mol/kg/H_2O
HCO_3^-	0.10481	61.0168	0.0017803
$B(OH)_3$	0.01944	61.8330	0.0003259
CO_3^{2-}	0.01434	60.0089	0.0002477
Sr^{2+}	0.00795	87.6200	0.0000940
$B(OH)_4^-$	0.00795	78.8404	0.0001045
F^-	0.00130	18.9984	0.0000709
CO_2	0.00042	44.0095	
OH^-	0.00014	17.0073	0.0000085
Total (major+minor)	**35.16504**		**1.1605659**
H_2O	**964.83496**		**0.580283**

Another parameter of primary importance for seawater products is osmolality. To define the exact osmolality, an in-house study was performed to test the exact osmolality of seawater preparations as a function of seawater content in the final product. Results are shown in the Table 3.

Table 3. Osmolality of the product depending on the seawater content

Osmolality [mOsm/kg]	Seawater content [%]
328	30.0
318	29.0
307	28.0
298	27.0
286	26.0
277	25.0
265	24.0
260	23.0
238	22.0
235	21.0
220	20.0

The results show that seawater in concentrations of approximately 26% to 27%, becomes hypertonic (considering plasma osmolality reference range of 285-295 mOsm/kg [10] and can exert a range of effects associated with hypertonic solutions.

3. Mechanism of action

The mechanism of action of saline/seawater solutions is based on two principles: physical and biological/physiological. The first principle is based on the physical (mechanical) effect of cleansing the nasal mucosa of the accumulated secretion and pathogens. The second principle depends on the effects of the ions on the physiology of the mucosal cells. In the Figure 1 we propose the chain of events following mucosal application of seawater preparations, resulting in a range of beneficiary effects.

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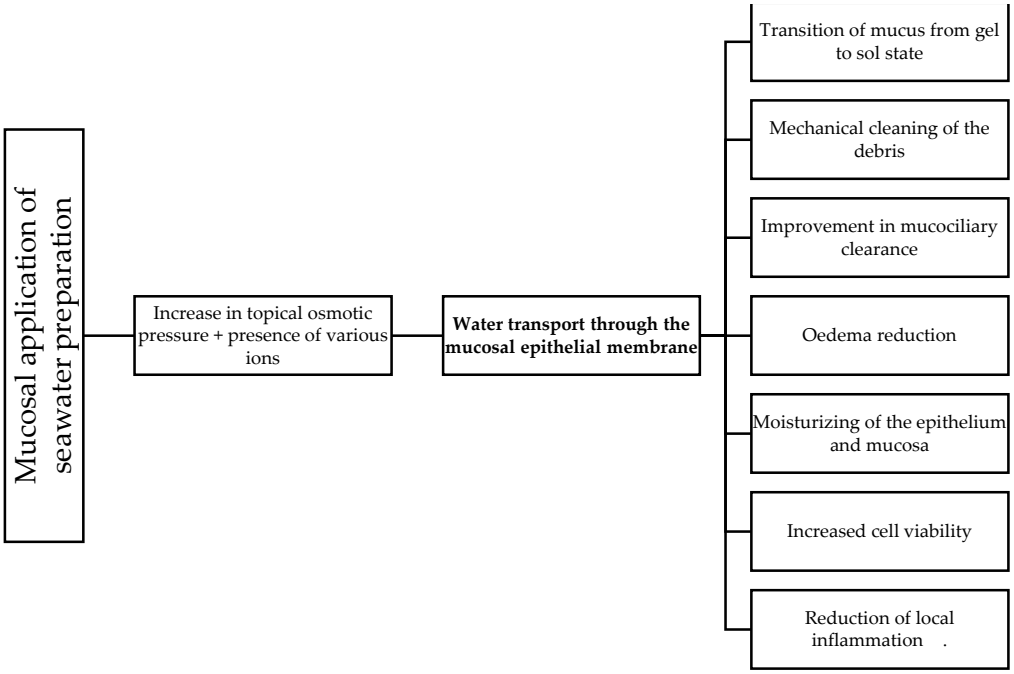

Figure 1. Proposed mechanism of action of seawater preparations locally applied to mucosa of the upper respiratory tract

Mechanism displayed in the Figure 1 above centres on the water transport through the mucosal epithelial membrane, provoked by the local application of hypertonic solution. Nasal mucosa is hydrated and moisturized by both local application of solution and influx of water through the membrane. Depending on the place of application, this leads to accumulation of liquid in the lumen and increased mucociliary clearance [11,12]. The mechanism has been proven both in vitro [13,14] and in vivo [15,16]. Reduction of swelling (oedema) is seen in submucosal tissue, while the immediate effect of excess liquid in nasal lumen is mechanical cleaning of mucus, crusts and debris. Imminently following is the change of the state of the mucus from gel to sol [17]. Transition of mucus from gel to sol state greatly reduces the amount of energy needed by cilia to transport such mucus [18], significantly improving efficacy of the mucociliary transport. Additional ionic constituents of seawater show other effects such as increased cell viability and inflammation reduction (Figure 1 and Table 4).

Indeed, the efficacy of mucociliary transport might be one of the key mechanisms how saline/seawater solutions exert their positive effect on the nasal tissue. Mucociliary transit time (MTT; the time needed for a compound to be transported a certain distance within the respiratory system), is used to assess the efficacy of mucociliary clearance. Compared to healthy volunteers with mean MTT of 12.01 +/- 3.0 minutes, this time is significantly prolonged in subjects with history of allergic rhinitis (15.5 +/- 3.5 minutes) and heavy smokers (16.5 +/- 5.0 minutes) [19]. Similarly, it has been shown that patients with a wide variety of diseases, ranging from septum deviations [20] to chronic sinusitis [21], have prolonged MTT and that the restoration of mucociliary clearance is of significant importance in treating the disease [22].

On the most basic level, MTT depends on the ciliary beat frequency (CBF). Wabnitz et al. used nasal sprays with 0.9% and 3.0% sodium chloride on eight healthy volunteers, having the mean baseline CBF of 9.6 Hz. While isotonic saline reduced the CBF first to 9.1 Hz (after 5 minutes) and 8.8 Hz (after one hour), use of 3.0% saline in-creased the CBF to 10.1 Hz before returning to near-baseline levels (9.2 Hz) at 60 minutes [23]. Similar results were seen by monitoring another parameter – saccharine clearance time, which decreased from median of 11.17 min to a median of 6.83 and 7.14 minutes after application of either

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isotonic or hypertonic saline, respectively [24]. These results, which show a beneficiary effect of hypertonic saline, but much smaller or completely absent effect of isotonic saline, are confirmed by other authors [25–28]. Same effects of hypertonic saline were shown for mucociliary clearance in asthmatic patients [29], subjects with cystic fibrosis [30–32], children with bronchiolitis [33] and healthy subjects [15]. On the molecular level, this effect seems to be based on the upregulation by the hypertonic saline of the CLC-3, a chloride channel that accounts for the transport of chloride ions in numerous tissues and plays a fundamental role in transepithelial salt and water movement [34].

Besides mentioned mechanism based on physical and osmotic effects of the solution, different ions contained in the seawater have a number of additional effects. These effects are displayed in the Table 4.

Table 4. Mechanism of action of other constituents seawater [3,35]

Constituent	Action
Mg^{2+}	Promotes cell repair and limits inflammation by reducing the eicosanoid metabolism both at the level of the liberation of arachidonic acid and by direct inhibition of the 5-lipoxygenase enzyme, Inhibits exocytosis from permeabilized eosinophils, Reduces apoptosis of respiratory cells.
Ca^{2+}	Acetylcholine and serotonin act as messengers, increasing calcium intake in ciliated cells and thus regulating ciliary beat frequency and synchronization, Airflow promotes cell calcium intake and ciliary beat via shear-stress-induced mechanotransduction.
K^{+}	Anti-inflammatory action, Promotes respiratory epithelium repair via the EGF/EGFR pathway.
HCO_3^{-}	Reduces mucous viscosity by acting as a buffer, Facilitates elimination by ciliary cells movement.

Mentioned findings show that, besides the immediate positive effect of the mechanical cleaning of the mucosal surface, there is an additional and potentially more important positive effect exerted through facilitating the physiological function of mucociliary transport achieved by the saline solution of adequate osmolality. Additionally, other ions contained in the solution show a wide range of beneficiary physiological effects on cellular level.

4. Aspects of saline/seawater in human use

The Table 5 shows main safety and efficacy conclusions from clinical trials and in-vitro studies, performed over more than 20 years. We searched MEDLINE, Scopus, Web of Science and Cochrane databases to identify studies of interest. The aim was to identify as much as possible relevant (especially clinical) studies. To achieve this, we used a broad search strategy, including only basic keywords of “seawater” and “saline”. For example, a MeSH search syntax was "Seawater"[Mesh] OR "Saline Solution"[Mesh] OR "Saline Solution, Hypertonic"[Mesh]. Considering that MeSH indexing takes some time, additional PubMed search with same keywords was performed for the studies published over the last three years. Additional studies were identified through Scopus and especially by following “Times Cited” links for the Web of Science results. After going through all the

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identified studies, we focused on the ones that, in our opinion, contribute most to the understanding of safety and efficacy aspects of saline/seawater use in human medicine. Covered are studies with both seawater and saline solutions in wide range of osmolalities and compositions. Safety and efficacy of these preparations will be shortly discussed here.

4.1. Safety

As it was already mentioned before, intranasal treatment with saline and sea-water preparations in form of either drops, spray, nebulizer or irrigation is considered to be very safe. Numerous studies, ranging from healthy individuals to infants and pregnant women, prove this point beyond a reasonable doubt. In Table 5, in more than 60 studies covering the period of last 23 years, general side effects are rare while serious ones virtually non-existent. Moreover, one must take into account the fact that in most of the studies subjects had at least one additional condition or diagnosis such as allergic rhinitis, rhinosinusitis, postoperative status, asthma, bronchiolitis etc. Most of these conditions require additional therapy which in itself could be the reason for side effect(s) ascribed to saline/seawater treatment. In the mentioned studies, in most cases adverse events are neither mentioned in the text of the papers or none were reported by study participants. In cases where adverse events have been mentioned, these were in most cases:

Burning feeling in nose and throat. Some studies report incidence of this adverse event to be rather high, so mild burning sensation was reported by majority (57% [29]) subjects in study by Kumar et al. In the same study, moderate burning was much less pronounced, with only 19% subjects reporting this side effect. Also, the intensity of burning seemed to be correlated to osmolality of the preparation, with hypertonic preparations causing more adverse events. Other studies report similar rated of burning among their participants, so Shoseyov et al. [36] describe burning in 4 (of total of 34) paediatric subjects with chronic sinusitis, with 3 taking hypertonic saline and one taking isotonic preparation (note similar rate of adverse events between hypertonic and isotonic groups, as described in the previous study). However, there are studies where this rate is inverse [37]. Other studies mentioning burning as a side effect of saline/seawater therapy either fall within incidence boundaries described above [38,39] or discuss burning as a side effect not affecting subjects' participation in the study or study's outcome [27,40–42].

Other adverse events were rare and include nasal drainage [40,43], epistaxis [41,44,45], bitter taste in mouth [41], pain [46] and nose dryness [47].

4.2. Efficacy

The efficacy of saline/seawater solutions has been proven in numerous clinical trials and studies, most of which are listed in the Tables 5 and 6. Efficacy has been proven in a variety of populations, from pregnant women and children to adults with a wide range of pathological conditions. Given that the attached list of publications speaks for itself, we will concentrate on presenting the essential facts about a few of the most important indications.

4.2.1. Chronic sinusitis

By definition, chronic rhinosinusitis (CRS) is an inflammation of the paranasal sinuses seen in several percent of both paediatric and adult population [48]. The diagnosis is based on the presence of at least 2 of 4 cardinal symptoms for at least 12 weeks and is confirmed by physical examination and (if necessary) additional radiological methods. Intranasal spray administration of corticosteroids is known to significantly improve symptoms, and a similar consensus exists for nasal saline irrigation. The use of oral antibiotics may be indicated in cases of acute exacerbations of the disease, although this was not corroborated in the recent Cochrane review on this topic [49]. Similar results have been described by a group of Russian authors in children [50].

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Papers listed in Tables 5 and 6 strongly confirm these findings. In paediatric population Pham et al. [51] have shown that 6-week treatment is well tolerated in children and is useful both as a first-line treatment for CRS and as an effective measure reducing the need for surgery. Regarding tonicity, in another paediatric study, hypertonic solution was shown to be comparable to the isotonic in terms of safety, although the number of adverse events was higher in the hypertonic group [36].

Evidence of both safety and efficacy are, expectedly, more numerous in adult population. Subjects treated with nasal saline used less antibiotics compared to the control group [52] and hypertonic solution was reported as superior to the isotonic solution [53–55]. Other hypertonic saline preparations such as the Dead Sea salt have also been proven as safe and effective in this indication [56]. While various application methods are used (mostly spray vs. low/large volume irrigation [43,57], the safety profile remains highly favourable across the various studies.

4.2.2. Allergic rhinitis

Allergic rhinitis is an extremely common condition that is also commonly overlooked in the diagnostic process, resulting in significant public health effects. Also, although it is not a severe illness, allergic rhinitis can significantly complicate symptoms, diagnosis and clinical course of other diseases [58].

Saline and specifically seawater preparations have been shown to be effective [59] and safe [60] as both long-term [61] and short term [62] treatments and to reduce the need for other commonly used treatment options such as antihistamines in children [63,64] and pregnant women [65]. The same was proven for the use of nasal steroids [66,67] and systemic drugs [68].

4.2.3. Other indications

Besides the two major indications listed above, there are numerous studies in other indications, as well as in vitro studies [69] and those performed on healthy participants, with latter serving primary as the proof of concept for safety and efficacy of nasal saline and seawater treatments.

Different methods of saline penetration were tested using the Technetium-99 labelled solution, with douching being the method with best penetration in the maxillary sinus [70]. Positive effects of nasal irrigation were proven in healthy army conscripts [47], adult subjects [14,23,71], and otherwise healthy subjects exposed to wood dust [44,72].

Regarding other indications, positive effects were described in paediatric patients with viral bronchiolitis [73], bronchiolitis in the intensive care unit [74], acute sinusitis [75], acute upper respiratory tract infections [76,77], chronic tonsilitis [78], cold and influenza [41]. Similar studies exist in adult subjects [79,80], including pregnant women [45]. Studies on postsurgical beneficiary effects of saline solutions [37,81], retrospective studies [82] as well as those based on questionnaires and surveys [42,83] seem to confirm all of the above mentioned effects.

4.2.4. Place of saline/seawater preparations in COVID-19 pandemic

Finally, although it is too early to speculate on whether the use of saline/seawater solutions has a place in preventing or reducing the symptoms of viral infections [84], a recent publication with people infected with coronavirus [80] suggests that this could be an interesting area of research in the near future. Also, there is a growing number of papers on this topic, suggesting potential positive effects of saline irrigations during the pandemic, both as preventive [86–88] and a treatment option [80]. A multidisciplinary group of Belgian authors in their recent paper [89] propose a detailed hypothesized mechanism of action of saline in coronavirus infections. The mechanism is quite similar to the one we

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propose in the present article including, among others, wetting properties to the local tissue, mucus gelling, and effects of the increased NaCl concentration on mucosa. Due to its effects described earlier in this paper and elsewhere [90], if used early and as an add-on therapy, locally applied saline/seawater solutions may represent an interesting and promising remedy for all viral infections, including SARS-CoV-2 [91].

Table 5. Overview of safety and efficacy conclusions from studies with saline and/or saltwater

Study	Design	Subjects	Intervention	Safety conclusions	Other remarks
Holmstrom, 1997 [44]	Cross-sectional	45 healthy adults exposed to wood dust	Nasal lavage with Rhinomer force 2, four times a day, every workday.	One increase in allergic symptoms (with concomitant local steroid). One anterior epistaxis and one throat irritation.	At week 3, 88% subjects wanted to continue treatment and 3 weeks after stopping treatment, 83% wished to start the treatment again.
Shoseyov, 1998 [36]	RCT	34 children with chronic sinusitis	Hypertonic (3.5%) vs. isotonic saline, 10 drops, three times daily for 4 weeks.	Three subjects in hypertonic and one in isotonic group left study because of the burning feeling in the nose and throat.	Burning and itching was more common in hypertonic group, but only during the first 3 to 4 days. After that period, there was no difference between the groups.
Rabone, 1999 [72]	Crossover trial with 1-year follow-up	46 woodworkers exposed to wood dust	Gravity fed, home-made unbuffered isotonic saline for 2 months.	Generally safe, no notable adverse events.	The group reported significantly decreased nasal symptoms and over half of subjects continued to use nasal lavage voluntarily after 1 year.
Taccariello, 1999 [91]	RCT	40 patients with chronic rhinosinusitis	Traditional alkaline nasal douche vs. a sterile sea water spray, in addition to their regular treatment.	No adverse effects mentioned.	Alkaline nasal douche had a significant effect upon endoscopic appearances, whereas the spray did not; conversely spray improved quality of life, whereas alkaline douche did not.
Bachmann, 2000 [71]	RCT	40 adults with paranasal sinus disease	Isotonic Ems salt solution or isotonic sodium chloride solution nasal irrigation twice daily for 7 days.	No adverse events mentioned in either group.	A slight difference between treatment with Ems salt solution and sodium chloride solution, questionable clinical relevance.
Heatley, 2001 [57]	Prospective RCT	150 adults with chronic rhinosinusitis	Nasal saline irrigation with bulb syringe or irrigation pot vs. placebo, daily for 2 weeks.	No significant adverse events; comparable efficacy in all three groups.	More than one-third of subjects reported using less concomitant medication.
Rabago, 2002 [52]	RCT	76 adults with acute or chronic rhinosinusitis	Nasal saline irrigation with 150 ml daily per nostril for 6 months vs. no treatment.	Ten side effects of which 8 were considered as "not significant" and 2 as significant but still were "highly satisfied" with the treatment.	Subjects treated with nasal saline used statistically significantly less antibiotic compared to control group.
Garavello, 2003 [63]	Prospective RCT	20 children with allergic rhinitis	Hypertonic saline in 10 subjects, no treatment in 10 subjects; 2.5 ml in each nostril three times daily for 6 weeks.	No patients lost to follow up and no adverse events reported.	Statistically significant decrease in use of oral antihistamines in hypertonic saline group.
Lee, 2003 [27]	RCT, crossover	28 healthy adult subjects	Hypertonic (Sinomarin, 3%) or	Conplainments of mild prickling sensation after	The effect of the hypertonic solution is probably due to

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			isotonic saline. 10 sprays of both preparations (on different days) in the same nostril.	nasal douching with hypertonic seawater.	changes in mucus viscoelastic properties.
Chkhartishvili, 2004 [68]	Case-control open clinical trial	30 children with allergic rhinitis, acute and chronic bacterial rhinosinusitis and 30 children in control group	"Aqua Maris" seawater solution, either irrigation or 2 drops in nasal cavity 3 times a day from 2 to 4 weeks.	Nasal drops in children up to 2 years of age were well tolerated, with no complication. No adverse effects mentioned for the irrigation group.	In subjects with bacterial rhinosinusitis time to relief of symptoms in Aqua Maris group was 7±3.2 days vs 10±2.4 days in control group. In allergic rhinitis group Aqua Maris reduced the use of systemic drugs in 7 of 15 patients.
Tano, 2004 [47]	Prospective trial	108 healthy army conscripts	10-week nasal spraying with physiological saline twice daily, followed by a 10-week period of follow up.	Two side effects of nose dryness.	There was a mean of 0.7 episodes of upper respiratory tract infection during the spray period, compared with 1.0 episodes during the observation.
Wormald, 2004 [70]	Prospective, crossover study	12 adult subjects	Nasal irrigation with normal saline containing Technetium 99m sulfur colloid	No adverse effects mentioned.	The nasal cavity was well irrigated three techniques (spray, nebulization, douching). Douching was significantly more effective in penetrating the maxillary sinus and frontal recess. The sphenoid and frontal sinuses were poorly irrigated by all three techniques.
Cordray, 2005 [92]	Prospective, randomized, single-blind, placebo-controlled	15 patients with seasonal allergic rhinitis	Intranasal hypertonic dead sea saline spray, intranasal aqueous triamcinolone spray, placebo nasal saline spray for 7 days.	Two subjects withdrew for adverse events (unknown group).	Active-treatments were superior to placebo, especially corticosteroids. Dead Sea saline solution improved mucociliary clearance while Mg cation probably exerted anti-inflammatory effects.
Garavello, 2005 [64]	Prospective RCT	44 children with allergic rhinitis	Hypertonic saline vs. no treatment; 3 sprays (50 μl) in each nostril three times daily for 7 weeks.	No adverse events in the treatment group.	Statistically significant decrease in use of oral antihistamines in hypertonic saline group.
Kim, 2005 [69]	In vitro study	Cell cultures of fully differentiated passage-2 normal human nasal epithelial cells	Cells in the cultures were treated with pure water and with 0.3% (hypotonic), 0.9% (isotonic) and 3% (hypertonic) saline solutions.	In vitro study.	mRNA for major airway mucins analysis and morphologic analysis suggests that pure water damaged epithelial cells and that only isotonic saline did not affect their morphology.
Passali, 2005 [79]	RCT	200 patients with acute viral rhinosinusitis	Atomized nasal douche, vs. nasal lavages with isotonic sodium chloride solution.	No adverse effects mentioned.	Atomized nasal douches significantly improved inspiratory and expiratory rhinomanometric resistance and

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					nasal volumes and normalized mucociliary transport time to a physiological level.
Wabnitz, 2005 [23]]	In-vitro study	8 healthy adult subjects	One application of four sprays of hypertonic (3.0%) saline (one nostril) and isotonic saline (another nostril) in all subjects.	No adverse effects mentioned.	Cell samples from subjects receiving saline solutions. The administration of hypertonic saline results in a significantly faster CBF 5 minutes (but not 60 minutes) after administration.
Friedman, 2006 [56]	Randomized, prospective, double-blind study	42 adults seeking treatment for chronic rhinosinusitis	Nasal irrigation using hypertonic dead sea salt solution with hypertonic saline.	No adverse effects mentioned.	Both groups had significant improvement after treatment. However, the dead sea salt patients had significantly better symptom relief and showed improved RQLQ(S) scores.
Rabago, 2006 [40]	Semi structured, in-depth interviews in a 3-part, multi-method study	28 subjects with frequent rhinosinusitis and chronic sinonasal symptoms.	Hypertonic saline nasal irrigation.	Side effects as saline drainage, nasal burning, or irritation were noted but not identified as important enough to stop the treatment.	This is a well-tolerated, inexpensive, effective, long-term therapy that patients can use at home with minimal training and follow-up.
Hauptman, 2007 [38]	RCT	80 adult patients with rhinosinusitis	1 ml of physiological or hypertonic saline to one nostril.	Increased nasal burning/irritation with hypertonic compared to physiological saline.	Buffered physiological saline significantly affected nasal airway patency, whereas buffered hypertonic saline had no effect on nasal patency.
Kuzik, 2007 [73]	Prospective, randomized, double-blinded, controlled, multicenter trial	96 infants with viral bronchiolitis	Repeated doses of nebulized 3% hypertonic saline or 0.9% normal saline, in addition to routine therapy.	All participants tolerated therapy without apparent adverse effects and were eventually discharged after achieving full recovery.	Clinically relevant reduction in length of stay to 2.6+/-1.9 days in hypertonic saline group, compared with 3.5+/-2.9 days in the normal saline group.
Pynnonen, 2007 [43]	Prospective RCT	127 adults with chronic nasal and sinus symptoms	Irrigation with large volume and low positive pressure or spray for 8 weeks.	Forty-one subjects reported a total of 67 adverse effects. Posttreatment nasal drainage was the most common adverse effect (n = 14) in each group.	Nasal irrigations performed with large volume and delivered with low positive pressure are more effective than saline sprays for treatment of chronic nasal and sinus symptoms in a community-based population.
Karpova, 2008 [78]	Open-label parallel-group trial	84 children with chronic tonsilitis	Experimental group with 64 subjects using Aqua Maris seawater solution and control group using furacilin solution for 6-8 courses of crypt lavage.	No adverse effects mentioned.	Aqua Maris group showed superior results in term of odynophagia and dysphagia severity and duration and hyperaemia and infiltration of the palatine arches.

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Slapak, 2008 [41]	Prospective RCT in parallel groups	401 children with cold or influenza	Nasal saline irrigation delivered via jet flow, fine spray or added to standard medication vs. standard medication alone. Applied 6 times daily in acute phase and 3 times daily for 12 weeks after.	At the second visit, only 8.7% patients recorded nasal wash complaints, and at the final visit, this dropped to 2.4%. The other reported complaints were burning, bitter taste and nose bleeding.	The saline treatment was well tolerated. Most complaints appeared in the medium jet group and were associated with the stronger flow of the wash.
Suslu, 2009 [37]	Prospective RCT	45 adult subjects after septoplasty	2.3% buffered hypertonic seawater, buffered isotonic saline, unbuffered isotonic saline; irrigation six times daily for 20 days.	No dropouts, no adverse events mentioned.	Buffered isotonic saline group had worse nasal burning VAS score when compared with both buffered hypertonic and nonbuffered isotonic saline solutions.
Ural, 2009 [93]	Observational	132 adult subjects	Control, allergic rhinitis, acute sinusitis and chronic sinusitis groups received two daily doses of hypertonic (3%) or isotonic nasal irrigation for 10 days.	No patients lost to follow up, and no serious side effects or intolerance necessitating cessation of irrigation reported.	Nasal irrigation with isotonic or hypertonic saline can improve mucociliary clearance time in various nasal pathologies.
Gelardi, 2009 [94]	Randomized pilot study	20 adult subjects with acute rhinosinusitis	A nasal syringe (10 mL saline solution, 3 times daily for 14 days) or the Lavonase system (250 mL saline solution sac, twice daily for 14 days).	No adverse effects mentioned.	Nasal irrigation with the Lavonase system was found to be more effective in reducing symptoms and decreasing nasal resistances.
Li, 2009 [66]	RCT	26 children with allergic rhinitis	Saline irrigation, steroid therapy, saline+steroid therapy groups; twice a day for 8 weeks.	No subjects lost to follow up, no adverse events in saline group.	Saline use permits use of less topical steroids in this indication.
Rabago, 2009 [42]	Electronic questionnaire	330 practicing family physicians in Wisconsin, US	Saline nasal irrigation for upper respiratory conditions.	Respondents were not queried directly about perceived safety profile of the treatment.	Analysis showed that 86.7% of respondents have used the treatment as adjunctive care for conditions including chronic rhinosinusitis (91%), acute bacterial rhinosinusitis (67%), seasonal allergic rhinitis (66%), viral upper respiratory infection (59%), other allergic rhinitis (48%), irritant based congestion (48%) and rhinitis of pregnancy (17%).

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Cingi, 2010 [59]	Prospective	100 adult subjects with allergic rhinitis	Seawater gel nasal spray in 4-hour intervals, two sprays per nostril, from morning till evening; for 10 days.	Gel was well-tolerated with no side-effects occurring.	Statistically significantly decreased rating of nasal congestion and discharge after the 10 day regimen.
Culig, 2010 [53]	RCT	60 patients with chronic rhinosinusitis	Isotonic vs hypertonic seawater spray solution, applied 3-6 times daily.	No adverse events were observed.	Hypertonic solution was statistically significant superior to the isotonic for all symptoms.
Hermelingmeier, 2012 [60]	Systematic review and meta-analysis	400 subjects of which 86 were children/adolescent and 45 were pregnant	Different treatments.	No adverse events mentioned, however not all studies included safety outcomes.	Saline nasal irrigation using isotonic solution can be recommended as complementary therapy in allergic rhinitis.
Satdhabudha, 2012 [95]	Prospective RCT	81 children with allergic rhinitis	Buffered hypertonic (1.25%) saline or isotonic saline; nasal irrigation 2 times daily for 4 weeks.	One subjects in each study group experienced nasal burning during the first use.	Satisfaction with nasal irrigation was comparable between groups.
Tantilipikorn, 2012 [39]	Prospective RCT	50 adult subjects with chronic rhinosinusitis after endoscopic surgery	Dexpanthenol (Mar Plus) vs. isotonic saline nasal sprays; 4 applications weekly on 1st, 2nd, 4th and 6th postoperative weeks.	Dropout rate was comparable between groups. Three subjects in nasal saline group reported burning sensation.	Product containing seawater (Mar Plus) had better efficacy and comparable safety to nasal saline.
Kumar, 2013 [54]	RCT	50 subjects with chronic sinusitis	Hypertonic (3.5%) or isotonic nasal saline; 10 drops, three times a day in both nostrils, for 4 weeks.	None of the patients' groups reported severe burning sensation. Mild burning sensation was reported by 14.3% in isotonic group and 57.1% in hypertonic group. Moderate burning sensation was reported by 19% of patients in hypertonic group.	Hypertonic saline nasal solution was more efficacious, well tolerated and it improved quality of life in patients.
Chen, 2014 [62]	Parallel design with 3 groups	61 children with allergic rhinitis	Nasal irrigation, intranasal corticosteroid, and combined treatment.	No adverse events reported by subjects.	Nasal irrigation and decreased nasal corticosteroids combination a significant improvement in symptoms and signs and a significant decrease in the mean eosinophile count in nasal secretions were observed at week 12.
Low, 2014 [81]	RCT	74 adult subjects after endoscopic sinus surgery	Normal saline, Ringer's solution and hypertonic saline group.	No adverse events mentioned.	All groups showed an improvement with treatment in SNOT-20 scores and VAS scores, as well as endoscopic evaluation of mucosa appearance over time but no improvement of MCC.

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Marchisio, 2014 [83]	Questionnaire sent by e-mail	860 primary care paediatricians	Nasal saline irrigation in preschool children.	98.3% of the participating physicians evaluated the treatment as effective and safe.	About 40% of physicians expressed doubts about parental compliance mainly because of a certain difficulty in administration or the supposed invasiveness of the procedure.
Nguyen, 2014 [67]	Prospective, unblinded, single-arm pilot study	40 subjects with allergic rhinitis	Large-volume low-pressure saline irrigation twice daily for 8 weeks to the ongoing regiment of nasal corticosteroids.	No adverse events reported.	Saline treatment significantly improved QOL, with no significant changes in nasal flows, pattern use of nasal steroids, or adverse events.
Pham, 2014 [51]	Retrospective cohort study and cross-sectional survey	144 children with paediatric chronic rhinosinusitis	6 weeks of once daily nasal irrigation.	The results of a long-term (median of 48 months) follow-up in 54 participants show treatment as safe and well-tolerated.	Nasal irrigation is effective as a first-line treatment for paediatric chronic rhinosinusitis and subsequent nasal symptoms, and reduces need for FESS and CT imaging.
Stoelzel, 2014 [96]	RCT	20 adult subjects with allergic rhinitis	Nasya/Prevalin (a thixotropic nasal gel) vs. isotonic seawater nasal spray; 2 sprays (2 × 0.14 mL) into each nostril.	No adverse events related to the application of the investigational product were recorded.	There was no difference between the two treatment groups regarding the global assessment of tolerability provided by the investigators or by the subjects.
Wang, 2014 [75]	Prospective, placebo-controlled RCT	60 atopic children with acute sinusitis	Standard treatment (including systemic antibiotics, mucolytics and nasal decongestants) with nasal irrigation with normal saline vs. standard treatment alone.	No significant side effects were recorded in the isotonic saline irrigation group.	There were significant improvements in mean PRQLQ and nPEFR values for the irrigation compared to the non-irrigation group. There was no significant difference in radiographic findings between the groups. The irrigation group recorded significant improvements in eye congestion, rhinorrhea, nasal itching, sneezing, and cough symptoms.
Alvarez-Puebla, 2015 [97]	CT	35 adults with asthma	Hypertonic saline (5%, administered by nebulizer) or mannitol.	Treatments were well tolerated.	Mannitol and hypertonic saline behaved similarly at sputum induction.
Koksal, 2016 [76]	Prospective, randomized double-blind trial	109 children under 2 years of age with acute upper respiratory infection	Saline nasal drops (0.9%), seawater nasal drops (2.3%) and control group (no treatment).	No adverse events mentioned.	No significant difference between saline and seawater groups in terms of nasal congestion but a significant difference between the control group and these two groups.
Bennett, 2015 [14]	RCT, open label, cross-over	12 healthy adults	Hypertonic saline; 2.8% NaCl, 4 ml.	No adverse events mentioned.	Inhaled 2.8% hypertonic saline in normal subjects was associated with a short-lived acceleration of MC, predominately in the central airways.

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Bonnomet, 2016 [13]	Randomized, controlled, blinded, in vitro study	Airway epithelial cells obtained from 13 nasal polyps' explants	Response (ciliary beat frequency and epithelial wound repair speed) of cells to 3 isotonic nasal irrigation solutions: normal saline 0.9%; non-diluted seawater; and 30% diluted seawater	In vitro study.	Non-diluted seawater obtains the best results on ciliary beat frequency and wound repair speed vs normal saline showing a deleterious effect on epithelial cell function.
Grasso, 2018 [61]	Prospective, controlled clinical trial	60 patients with allergic rhinitis	Daily, 5-month treatment with isotonic seawater nasal spray enriched with manganese (4 puffs/day).	No adverse events mentioned.	The treatment significantly decreased the number of episodes of acute allergic rhinitis and increased QOL without the adverse effects of the standard care therapy.
Bergmann, 2019 [45]	Uncontrolled, prospective, longitudinal CT	136 patients with disorders of nose and paranasal sinuses including 11 pregnant women and one nursing mother	Seawater nasal spray (2.7%).	One adverse event reported (epistaxis).	Over the study period (mean 44 days) statistically significant reductions in 10 out of 12 symptoms was found. Only for parameters "impairment of taste" and "impairment of food intake" no significant change in symptoms was observed.
Bogomil'skij, 2019 [77]	Uncontrolled, prospective, longitudinal CT	Children aged 2-5 years with acute infectious rhinitis (some with viral comorbidity)	Aqua Maris spray.	None reported.	Rapid regression of symptoms such as nasal congestion and snoring, a decrease in the amount of nasal discharge by the 3rd day from the start of drug use and normalization of the rhinoscopic findings by 5-7th day of treatment.
Stobbelaar, 2019 [74]	Retrospective study	104 children up to 2 years of age with bronchiolitis in intensive care unit	Nebulised hypertonic saline.	No adverse events mentioned.	In respiratory syncytial virus positive patients, the use of nebulised hypertonic saline was correlated with a decrease in the duration of respiratory support and the length of stay by factors 0.72 and 0.81, respectively.
Craig, 2019 [98]	Prospective, randomised, controlled, double-blind, superiority trial	107 children aged 6 months to 5 years planned to have a nasogastric tube inserted in emergency department	Lidocaine and phenylephrine nasal spray or 0.9% sodium chloride placebo nasal spray, before nasogastric insertion	Adverse effects occurred in 28% of those who received lidocaine and phenylephrine and 42% of those who received placebo.	Lidocaine and phenylephrine nasal spray does not reduce procedure-related distress associated with nasogastric tube insertion in young children compared with saline.
Perić, 2019[55]	Prospective, randomized study	30 patients with Aspirin-induced chronic rhinosi-	Hypertonic (2.3% NaCl) sea water and isotonic 0.9% NaCl.	Nasal discomforts were detected in two patients in hypertonic sea water	Significantly lower total symptom score during the 7th, 14th, 21st and the 28th day, lower total endoscopic score on the 21st and 28th

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		nusitis undergoing endoscopic sinus surgery		group and in two patients in the isotonic group.	day, lower nasal obstruction, facial pain/pressure, headache and trouble sleeping, and lower nasal mucosal oedema, nasal secretion and nasal crusting in patients treated by hypertonic sea water.
Ramalingam, 2020 [80]	Post-hoc secondary analysis of data from the Edinburgh and Lothians Viral Intervention Study	66 adults with upper respiratory tract infection	The intervention group used hypertonic saline at home and performed nasal irrigation and gargling up to 12 times/day. Control arm participants did not use a specific treatment.	None mentioned.	The duration of illness was shorter in the intervention arm in the subset of patients infected with coronavirus (mean 5.6 vs. 8.1 days). The difference in the duration of blocked nose was -3.1 days, cough -3.3 days and hoarseness of voice -2.9 days in favour of hypertonic saline treatment.
Huang, 2021 [99]	In vitro	A 3D reconstituted human nasal epithelium model, mixture of human nasal cells isolated from 14 donors.	Seawater preparation (Stérimar Nasal Hygiene), tissue integrity via transepithelial electrical resistance was measured.	In vitro study.	Treatment did not compromise the integrity of the nasal epithelium in vitro but was effective for removal of foreign particles through MCC increase and for enhancing wound repair on nasal mucosa.
Jiang, 2021 [100]	Multicentre retrospective cohort trial	144 adult subjects with upper respiratory tract infections	Non-drug supportive treatment vs. supportive treatment and nasal irrigation with sea salt-derived physiological saline.	No adverse events reported.	Seawater group was statistically significantly superior in terms of nasal congestion, nasal discharge, sleep quality and appetite, but not for cough and fatigue.

Table 6. Overview of review articles with saline and/or saltwater

Study	Design	Indication(s)	Intervention(s)	Remarks
Papsin, 2003 [101]	Literature review	Rhinosinusitis, allergic rhinitis, postoperative irrigation, common cold	Nasal irrigation as an adjunct treatment	The procedure has been used safely by both adults and children and has no documented serious adverse effects. Trials indicate that patients treated with nasal irrigation rely less on other medications and that some postsurgical patients tend to require fewer visits to physicians. Both effects are likely to have desirable economic consequences for patients and the health care system.
Brown, 2004 [102]	Literature review	(Chronic) sinusitis, sinonasal conditions, rhinitis, postoperative patients	Isotonic and hyperthonic saline, buffered/unbuffered solutions, additives such as antibacterial or antifungal agents, home recipes vs. manufactured solutions	Nasal irrigations are an important component in the management of most sinonasal conditions. Authors note on disparity of opinion about the effects of irrigations on ciliary beat frequency and mucociliary clearance and controversy concerning irrigation tonicity and the use of additives to the irrigating solution.

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Study	Design	Indication(s)	Intervention(s)	Remarks
Harvey, 2007 [103]	Review (Cochrane)	Chronic sinusitis	Randomised controlled trials in which saline was evaluated in comparison with either no treatment, a placebo, as an adjunct to other treatments or against treatments. The comparison of hypertonic versus isotonic solutions.	Saline irrigations are well tolerated. Although minor side effects are common, the beneficial effect of saline appears to outweigh these drawbacks for the majority of patients. The use of topical saline could be included as a treatment adjunct for the symptoms of chronic rhinosinusitis.
Kassel, 2010 [104]	Review (Cochrane)	Upper respiratory tract infections	RCTs comparing topical nasal saline treatment to other interventions in adults and children with clinically diagnosed acute URTIs.	Three RCTs (618 participants) were included. Most results showed no difference between nasal saline treatment and control. However, there was limited evidence of benefit with nasal saline irrigation in adults. Minor discomfort was not uncommon and 40% of babies did not tolerate nasal saline drops.
Zhang, 2008 [105]	Review (Cochrane)	Acute bronchiolitis in infants	Nebulized hypertonic saline alone or in conjunction with bronchodilators as an active intervention in infants with acute bronchiolitis.	Current evidence suggests nebulized 3% saline may significantly reduce the length of hospital stay among infants hospitalized with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.
Adappa, 2012 [106]	Literature review	Rhinosinusitis	Saline irrigation (hypertonic vs. physiologic), Saline spray, antibiotics, topical steroids, topical antifungal treatment, anti IL-5 treatment	Physiologic saline irrigation is beneficial in the treatment of symptoms of CRS. Low-level evidence supports the effectiveness of topical antibiotics in the treatment of CRS. The use of topical antifungals is not supported by the majority of studies. Intranasal steroids are beneficial in the treatment of CRS with nasal polyposis. There is insufficient evidence to demonstrate a clear overall benefit for topical steroids in CRS without nasal polyposis.
Chirico, 2014 [107]	Literature review	Nasal congestion in infants and children	Nasal saline	The use of isotonic and hypertonic saline solutions is a valuable non-pharmacological treatment for nasal congestion in children, especially by improving mucociliary clearance and reducing the use of medications (antihistamines, decongestants, antibiotics, corticosteroids) during the treatment of URTIs. They are well tolerated and can be recommended for infants.
Bastier, 2015 [35]	Overview of randomized clinical trials	Different sinonasal pathologies and postoperative care	Different treatments compared to nasal irrigation including rhinocorticoids, antihistamines, buffered, unbuffered, alkaline, hyper- and isotonic saline	Large-volume low-pressure nasal irrigation using undiluted seawater seems, in the present state of knowledge, to be the most effective protocol.
Chong, 2016 [49]	Review (Cochrane)	Chronic rhinosinusitis	Studies with follow-up period of at least three months comparing saline delivered to the nose by any means (douche, irrigation, drops, spray or nebuliser) with placebo, no treatment or other pharmacological interventions	The evidence suggests that there is no benefit of a low-volume nebulised saline spray over intranasal steroids. There is some benefit of daily, large-volume (150 ml) saline irrigation with a hypertonic solution when compared with placebo.
Baron, 2016 [33]	Literature review	Bronchiolitis in infants	Hypertonic saline	Authors agree with the AAP guidelines regarding the use of nebulized hypertonic saline to reduce bronchiolitis scores and length of stay for infants with bronchiolitis who are expected to be hospitalized for more than 72 hours.

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Study	Design	Indication(s)	Intervention(s)	Remarks
Madison, 2016 [108]	Literature review	Allergic rhinitis in children	Nasal saline irrigation vs. intranasal corticosteroids	Intranasal steroids are more effective than nasal saline alone to reduce symptoms of allergic rhinitis in children. However, combination therapy further improves symptom reduction.
Kanjanawasee, 2018 [109]	Systematic search with Ovid MEDLINE, Scopus, PubMed and Google Scholar	Sinonasal diseases, including rhinitis and rhinosinusitis	Hypertonic vs. isotonic saline	Nine studies (740 patients) were included. Hypertonic nasal irrigation brought greater benefits over isotonic in symptom reduction; however, no difference was shown in SNOT-20 improvement. Effects favouring hypertonic solution on symptoms were larger in patients with rhinitis compared with rhinosinusitis; patients under the age of 18 years; saline irrigation using high volume compared with low volume and saline irrigation with hypertonicity of < 3% and hypertonicity of 3%-5% compared with hypertonicity of >5%. No major adverse effects were reported.
Li, 2019 [110]	Systematic review and meta-analysis literature following the PRISMA guidelines	Allergic rhinitis in children	Hypertonic saline nasal irrigation	Hypertonic saline treatment improved patients' nasal symptom scores and significantly lower rescue antihistamine use rate. Analyses comparing hypertonic with isotonic saline nasal irrigation better nasal symptom scores in hypertonic group, although the antihistamine use and adverse effect rates were similar between groups.
King, 2019 [111]	Literature review with evidence for each of the indications	Chronic sinusitis, allergic rhinitis, acute URTI	Saline solutions, dependent on the indication studied	Saline nasal irrigation is recommended as an adjunct therapy for common colds/rhinosinusitis, chronic sinusitis, allergic rhinitis and after nasal surgery. It appears to be safe and generally well tolerated, even for children. The use of SNI has the potential to reduce the number of antibiotic prescriptions for acute and chronic sinus infections, and improve outcomes for patients.

5. Conclusions

Saline solutions eq Aqua Maris show numerous positive effects in clinical use in upper respiratory tract. These are mainly mechanical (cleaning of the mucosa) and related to osmolality (oedema reduction and moisturizing of the epithelium). In our paper we present a comprehensive body of evidence why sea-water is superior to saline for SNI in general as well as for the wide variety of clinical indications such as infectious diseases of the upper respiratory tract, allergic rhinitis, postoperative care etc. Due to its chemical constituents such as magnesium, calcium, potassium, bicarbonate and other ions, seawater shows a range of additional chemical effects from promoting cell repair and reducing inflammation to reducing viscosity of the mucus and increasing ciliary beat frequency. Numerous studies in URT patients, healthy volunteers, pregnant women, children and elderly prove exceptionally good safety profile of seawater preparations. Side effects are rare and consist mostly of burning feeling and nasal drainage, with serious adverse events practically non-existent.

To the best of our knowledge, a scientifically proven consensus on the exact mechanism of action of seawater in human upper respiratory tract does not exist. Therefore, and based on the comprehensive literature search, we propose a mechanism of action that considers all the different aspects of sea-water solution(s), from chemical composition to pH and tonicity.

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1. Meera, S.; Vandana Rani, M.; Sreedhar, C.; Robin, D.T. A Review on the Therapeutic Effects of NetiKriya with Special Reference to JalaNeti. *Journal of Ayurveda and integrative medicine* **2020**, *11*, 185–189, doi:10.1016/J.JAIM.2018.06.006.
2. Khianey, R.; Oppenheimer, J. Is Nasal Saline Irrigation All It Is Cracked up to Be? *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* **2012**, *109*, 20–28, doi:10.1016/J.ANAI.2012.04.019.
3. Principi, N.; Esposito, S. Nasal Irrigation: An Imprecisely Defined Medical Procedure. *International journal of environmental research and public health* **2017**, *14*, doi:10.3390/IJERPH14050516.
4. Ho, E.Y.; Cady, K.A.; Robles, J.S. A Case Study of the Neti Pot's Rise, Americanization, and Rupture as Integrative Medicine in U.S. Media Discourse. *Health communication* **2016**, *31*, 1181–1192, doi:10.1080/10410236.2015.1047145.
5. Lyman, J.; Fleming, R.H. *Composition of Sea Water*; J. mar. Res., 1940; Vol. 3(2);
6. Cox, R.A.; Culkin, F.; Riley, J.P.; Cox, R.A.; Culkin, F.; Riley, J.P. The Electrical Conductivity/Chlorinity Relationship in Natural Sea Water. *DSRA* **1967**, *14*, 203–220, doi:10.1016/0011-7471(67)90006-X.
7. Morris, A.W.; Riley, J.P. The Bromide/Chlorinity and Sulphate/Chlorinity Ratio in Sea Water. *Deep Sea Research and Oceanographic Abstracts* **1966**, *13*, 699–705, doi:10.1016/0011-7471(66)90601-2.
8. Millero, F.J. *Chemical Oceanography*; 4th ed.; CRC Press: Boca Raton, 2013;
9. Štanfel, D. Comparasion of Ion Chromatography with Other Methods in Sea Water Analysis of the Adriatic Coast, Zagreb, 2006.
10. Bhalla, A.; Sankaralingam, S.; Dundas, R.; Swaminathan, R.; Wolfe, C.D.A.; Rudd, A.G. Influence of Raised Plasma Osmolality on Clinical Outcome after Acute Stroke. *Stroke* **2000**, *31*, 2043–2048, doi:10.1161/01.STR.31.9.2043.
11. Daviskas, E.; Anderson, S.D.; Gonda, I.; Eberl, S.; Meikle, S.; Seale, J.P.; Bautovich, G. Inhalation of Hypertonic Saline Aerosol Enhances Mucociliary Clearance in Asthmatic and Healthy Subjects. *The European respiratory journal* **1996**, *9*, 725–732, doi:10.1183/09031936.96.09040725.
12. Trimble, A.T.; Whitney Brown, A.; Laube, B.L.; Lechtzin, N.; Zeman, K.L.; Wu, J.; Ceppe, A.; Waltz, D.; Bennett, W.D.; Donaldson, S.H. Hypertonic Saline Has a Prolonged Effect on Mucociliary Clearance in Adults with Cystic Fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* **2018**, *17*, 650–656, doi:10.1016/J.JCF.2018.01.001.
13. Bonnomet, A.; Luczka, E.; Coraux, C.; de Gabory, L. Non-Diluted Seawater Enhances Nasal Ciliary Beat Frequency and Wound Repair Speed Compared to Diluted Seawater and Normal Saline. *International forum of allergy & rhinology* **2016**, *6*, 1062–1068, doi:10.1002/ALR.21782.

14. Bennett, W.D.; Wu, J.; Fuller, F.; Balcazar, J.R.; Zeman, K.L.; Duckworth, H.; Donn, K.H.; O'Riordan, T.G.; Boucher, R.C.; Donaldson, S.H. Duration of Action of Hypertonic Saline on Mucociliary Clearance in the Normal Lung. *Journal of applied physiology (Bethesda, Md.: 1985)* **2015**, *118*, 1483–1490, doi:10.1152/JAPPLPHYSIOL.00404.2014.
15. Pavia, D.; Thomson, M.L.; Clarke, S.W. Enhanced Clearance of Secretions from the Human Lung after the Administration of Hypertonic Saline Aerosol. *The American review of respiratory disease* **1978**, *117*, 199–203, doi:10.1164/ARRD.1978.117.2.199.
16. Donaldson, S.H.; Bennett, W.D.; Zeman, K.L.; Knowles, M.R.; Tarran, R.; Boucher, R.C. Mucus Clearance and Lung Function in Cystic Fibrosis with Hypertonic Saline. *The New England journal of medicine* **2006**, *354*, 241–250, doi:10.1056/NEJMOA043891.
17. Quraishi, M.S.; Jones, N.S.; Mason, J. The Rheology of Nasal Mucus: A Review. *Clinical otolaryngology and allied sciences* **1998**, *23*, 403–413, doi:10.1046/J.1365-2273.1998.00172.X.
18. Sleigh, M.A. Ciliary Adaptations for the Propulsion of Mucus. *Biorheology* **1990**, *27*, 527–532, doi:10.3233/BIR-1990-273-431.
19. Mahakit, P.; Pumhlrun, P. A Preliminary Study of Nasal Mucociliary Clearance in Smokers, Sinusitis and Allergic Rhinitis Patients. *Asian Pacific Journal of Allergy and Immunology* **1995**, *13*, 119–121.
20. Passàli, D.; Ferri, R.; Becchini, G.; Passàli, G.C.; Bellussi, L. Alterations of Nasal Mucociliary Transport in Patients with Hypertrophy of the Inferior Turbinates, Deviations of the Nasal Septum and Chronic Sinusitis. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* **1999**, *256*, 335–337, doi:10.1007/S004050050158.
21. Ohashi, Y.; Nakai, Y. Reduced Ciliary Action in Chronic Sinusitis. *http://dx.doi.org/10.3109/00016488309105583* **2009**, *95*, 3–9, doi:10.3109/00016488309105583.
22. Hafner, B.; Davris, S.; Riechelmann, H.; Mann, W.J.; Amedee, R.G. Endonasal Sinus Surgery Improves Mucociliary Transport in Severe Chronic Sinusitis. *American journal of rhinology* **1997**, *11*, 271–274, doi:10.2500/105065897781446612.
23. Wabnitz, D.A.M.; Wormald, P.J. A Blinded, Randomized, Controlled Study on the Effect of Buffered 0.9% and 3% Sodium Chloride Intranasal Sprays on Ciliary Beat Frequency. *The Laryngoscope* **2005**, *115*, 803–805, doi:10.1097/01.MLG.0000157284.93280.F5.
24. Homer, J.J.; England, R.J.; Wilde, A.D.; Harwood, G.R.J.; Stafford, N.D. The Effect of PH of Douching Solutions on Mucociliary Clearance. *Clinical otolaryngology and allied sciences* **1999**, *24*, 312–315, doi:10.1046/J.1365-2273.1999.00265.X.
25. Talbot, A.R.; Herr, T.M.; Parsons, D.S. Mucociliary Clearance and Buffered Hypertonic Saline Solution. *The Laryngoscope* **1997**, *107*, 500–503, doi:10.1097/00005537-199704000-00013.
26. Wen, Z.; Wu, C.; Cui, F.; Zhang, H.; Mei, B.; Shen, M. The Role of Osmolality in Saline Fluid Nebulization after Tracheostomy: Time for Changing? *BMC Pulmonary Medicine* **2016**, *16*, 1–10, doi:10.1186/S12890-016-0342-X/FIGURES/5.
27. Lee, S.H.; Song, J.S.; Lee, S.H.; Hwang, S.J.; Lee, H.M. Effect of Hypertonic Seawater (Sinomarin(R)) on Mucociliary Clearance in Normal Subjects. *Journal of Rhinology* **2016**, *10*, 19–22.

28. Keojampa, B.K.; Hoang Nguyen, M.; Ryan, M.W. Effects of Buffered Saline Solution on Nasal Mucociliary Clearance and Nasal Airway Patency. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* **2004**, *131*, 679–682, doi:10.1016/J.OTOHNS.2004.05.026.
29. Daviskas, E.; Anderson, S.D.; Gonda, I.; Eberl, S.; Meikle, S.; Seale, J.P.; Bautovich, G. Inhalation of Hypertonic Saline Aerosol Enhances Mucociliary Clearance in Asthmatic and Healthy Subjects. *The European respiratory journal* **1996**, *9*, 725–732, doi:10.1183/09031936.96.09040725.
30. Eng, P.; Morton, J.; Douglass, J.; Riedler, J.; Wilson, J.; Robertson, C. Short-term Efficacy of Ultrasonically Nebulized Hypertonic Saline in Cystic Fibrosis. *undefined* **1996**, doi:10.1002/(SICI)1099-0496(199602)21:2.
31. Stahl, M.; Wielpütz, M.O.; Ricklefs, I.; Dopfer, C.; Barth, S.; Schlegtendal, A.; Graeber, S.Y.; Sommerburg, O.; Diekmann, G.; Hüsing, J.; et al. Preventive Inhalation of Hypertonic Saline in Infants with Cystic Fibrosis (PRESIS). A Randomized, Double-Blind, Controlled Study. *American journal of respiratory and critical care medicine* **2019**, *199*, 1238–1248, doi:10.1164/RCCM.201807-1203OC.
32. Robinson, M.; Hemming, A.L.; Regnis, J.A.; Wong, A.G.; Bailey, D.L.; Bautovich, G.J.; King, M.; Bye, P.T.P. Effect of Increasing Doses of Hypertonic Saline on Mucociliary Clearance in Patients with Cystic Fibrosis. *Thorax* **1997**, *52*, 900–903, doi:10.1136/THX.52.10.900.
33. Baron, J.; El-Chaar, G. Hypertonic Saline for the Treatment of Bronchiolitis in Infants and Young Children: A Critical Review of the Literature. *The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG* **2016**, *21*, 7–26, doi:10.5863/1551-6776-21.1.7.
34. Li, H. bin; Shi, J. bo; Cao, F.; Cheng, L.; Wen, W. ping; Xu, G. Hypertonic Saline Solution Stimulated CLC-3 Production in Primary Cultured Human Nasal Epithelial Cells. *Auris, nasus, larynx* **2008**, *35*, 47–51, doi:10.1016/J.ANL.2007.04.015.
35. Bastier, P.L.; Lechot, A.; Bordenave, L.; Durand, M.; de Gabory, L. Nasal Irrigation: From Empiricism to Evidence-Based Medicine. A Review. *European annals of otorhinolaryngology, head and neck diseases* **2015**, *132*, 281–285, doi:10.1016/J.ANORL.2015.08.001.
36. Shoseyov, D.; Bibi, H.; Shai, P.; Shoseyov, N.; Shazberg, G.; Hurvitz, H. Treatment with Hypertonic Saline versus Normal Saline Nasal Wash of Pediatric Chronic Sinusitis. *The Journal of allergy and clinical immunology* **1998**, *101*, 602–605, doi:10.1016/S0091-6749(98)70166-6.
37. Süslü, N.; Bajin, M.D.; Süslü, A.E.; Öğretmenoğlu, O. Effects of Buffered 2.3%, Buffered 0.9%, and Non-Buffered 0.9% Irrigation Solutions on Nasal Mucosa after Septoplasty. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* **2009**, *266*, 685–689, doi:10.1007/S00405-008-0807-5.
38. Hauptman, G.; Ryan, M.W. The Effect of Saline Solutions on Nasal Patency and Mucociliary Clearance in Rhinosinusitis Patients. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* **2007**, *137*, 815–821, doi:10.1016/J.OTOHNS.2007.07.034.
39. Tantilipikorn, P.; Tunsuriyawong, P.; Jareoncharsri, P.; Bedavanija, A.; Assanasen, P.; Bunnag, C.; Metheetrairut, C. A Randomized, Prospective, Double-Blind Study of the Efficacy of Dexpanthenol Nasal Spray on the Postoperative Treatment of Patients with Chronic Rhinosinusitis after Endoscopic Sinus Surgery. *J Med Assoc Thai* **2012**, *95*, 58–63.
40. Rabago, D.; Barrett, B.; Marchand, L.; Maberry, R.; Mundt, M. Qualitative Aspects of Nasal Irrigation Use by Patients with Chronic Sinus Disease in a Multimethod Study. *Annals of family medicine* **2006**, *4*, 295–301, doi:10.1370/AFM.552.

41. Šlapak, I.; Skoupá, J.; Strnad, P.; Horník, P. Efficacy of Isotonic Nasal Wash (Seawater) in the Treatment and Prevention of Rhinitis in Children. *Archives of otolaryngology--head & neck surgery* **2008**, *134*, 67–74, doi:10.1001/ARCHOTO.2007.19.
42. Rabago, D.; Zgierska, A.; Peppard, P.; Bamber, A. The Prescribing Patterns of Wisconsin Family Physicians Surrounding Saline Nasal Irrigation for Upper Respiratory Conditions. *WMJ : official publication of the State Medical Society of Wisconsin* **2009**, *108*, 145.
43. Pynnonen, M.A.; Mukerji, S.S.; Kim, H.M.; Adams, M.E.; Terrell, J.E. Nasal Saline for Chronic Sinonasal Symptoms: A Randomized Controlled Trial. *Archives of otolaryngology--head & neck surgery* **2007**, *133*, 1115–1120, doi:10.1001/ARCHOTOL.133.11.1115.
44. Holmström, M.; Rosén, G.; Wåhlander, L. Effect of Nasal Lavage on Nasal Symptoms and Physiology in Wood Industry Workers. *Rhinology* **1997**, *35*, 108–112.
45. Bergmann, C.; Müller, K.; Thieme, U.; Zeman, F.; Huppertz, G.; Koller, M.; Meiser, P. Real-World Data on the Use of Hypertonic Saline Nasal Spray in ENT Practice. *SN Comprehensive Clinical Medicine 2019 1:5* **2019**, *1*, 354–361, doi:10.1007/S42399-019-0050-Y.
46. Chusakul, S.; Warathanasin, S.; Suksangpanya, N.; Phannaso, C.; Ruxrungtham, S.; Snidvongs, K.; Aeumjaturapat, S. Comparison of Buffered and Nonbuffered Nasal Saline Irrigations in Treating Allergic Rhinitis. *The Laryngoscope* **2013**, *123*, 53–56, doi:10.1002/LARY.23617.
47. Tano, L.; Tano, K. A Daily Nasal Spray with Saline Prevents Symptoms of Rhinitis. *Acta oto-laryngologica* **2004**, *124*, 1059–1062, doi:10.1080/00016480410017657.
48. Halawi, A.M.; Smith, S.S.; Chandra, R.K. Chronic Rhinosinusitis: Epidemiology and Cost. *Allergy and asthma proceedings* **2013**, *34*, 328–334, doi:10.2500/AAP.2013.34.3675.
49. Chong, L.Y.; Head, K.; Hopkins, C.; Philpott, C.; Glew, S.; Scadding, G.; Burton, M.J.; Schilder, A.G.M. Saline Irrigation for Chronic Rhinosinusitis. *The Cochrane database of systematic reviews* **2016**, *4*, doi:10.1002/14651858.CD011995.PUB2.
50. Radtsig, E.; Ermilova, N. v; Bogomilskiy, M.R. Nose Obstruction in Children: Causes and Methods of Treatment. *Pediatrija. Žurnal IM. G.N. Speranskogo* **2012**, *91*, 85–90.
51. Pham, V.; Sykes, K.; Wei, J. Long-Term Outcome of Once Daily Nasal Irrigation for the Treatment of Pediatric Chronic Rhinosinusitis. *The Laryngoscope* **2014**, *124*, 1000–1007, doi:10.1002/LARY.24224.
52. Rabago, D.; Zgierska, A.; Mundt, M.; Barrett, B.; Bobula, J.; Maberry, R. Efficacy of Daily Hypertonic Saline Nasal Irrigation among Patients with Sinusitis: A Randomized Controlled Trial. *The Journal of family practice* **2002**, *51*, 1049–1055.
53. Culig, J.; Leppée, M.; Vceva, A.; Djanic, D. Efficiency of Hypertonic and Isotonic Seawater Solutions in Chronic Rhinosinusitis. *Med Glas (Zenica)* **2010**, *7*, 116–123.
54. Kumar, R.A..; Viswanatha, B.; Krishna, N.; Jayanna, N.; Shetty, D.R. Efficacy of Hypertonic Saline and Normal Saline in the Treatment of Chronic Sinusitis. *Int J Otolaryn Head Neck Surg* **2013**, *2*, 90–96.
55. Perić, A.; Kovačević, S.V.; Barać, A.; Gaćeša, D.; Perić, A. v.; Jožin, S.M. Efficacy of Hypertonic (2.3%) Sea Water in Patients with Aspirin-Induced Chronic Rhinosinusitis Following Endoscopic Sinus Surgery. *Acta oto-laryngologica* **2019**, *139*, 529–535, doi:10.1080/00016489.2019.1605454.
56. Friedman, M.; Vidyasagar, R.; Joseph, N. A Randomized, Prospective, Double-Blind Study on the Efficacy of Dead Sea Salt Nasal Irrigations. *The Laryngoscope* **2006**, *116*, 878–882, doi:10.1097/01.MLG.0000216798.10007.76.

57. Heatley, D.G.; McConnell, K.E.; Kille, T.L.; Leverson, G.E. Nasal Irrigation for the Alleviation of Sinonasal Symptoms. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery* **2001**, *125*, 44–48, doi:10.1067/MHN.2001.115909.
58. Greiner, A.N.; Hellings, P.W.; Rotiroti, G.; Scadding, G.K. Allergic Rhinitis. *Lancet (London, England)* **2011**, *378*, 2112–2122, doi:10.1016/S0140-6736(11)60130-X.
59. Cingi, C.; Halis Unlu, H.; Songu, M.; Yalcin, S.; Topcu, I.; Cakli, H.; Bal, C. Seawater Gel in Allergic Rhinitis: Entrapment Effect and Mucociliary Clearance Compared with Saline. *Therapeutic advances in respiratory disease* **2010**, *4*, 13–18, doi:10.1177/1753465809358190.
60. Hermelingmeier, K.E.; Weber, R.K.; Hellmich, M.; Heubach, C.P.; Mösges, R. Nasal Irrigation as an Adjunctive Treatment in Allergic Rhinitis: A Systematic Review and Meta-Analysis. *American journal of rhinology & allergy* **2012**, *26*, doi:10.2500/AJRA.2012.26.3787.
61. Grasso, M.; de Vincentiis, M.; Agolli, G.; Cilurzo, F.; Grasso, R. The Effectiveness of Long-Term Course of Sterimar Mn Nasal Spray for Treatment of the Recurrence Rates of Acute Allergic Rhinitis in Patients with Chronic Allergic Rhinitis. *Drug design, development and therapy* **2018**, *12*, 705–709, doi:10.2147/DDDT.S145173.
62. Chen, J.R.; Jin, L.; Li, X.Y. The Effectiveness of Nasal Saline Irrigation (Seawater) in Treatment of Allergic Rhinitis in Children. *International journal of pediatric otorhinolaryngology* **2014**, *78*, 1115–1118, doi:10.1016/J.IJPORL.2014.04.026.
63. Garavello, W.; Romagnoli, M.; Sordo, L.; Gaini, R.M.; di Berardino, C.; Angrisano, A. Hypersaline Nasal Irrigation in Children with Symptomatic Seasonal Allergic Rhinitis: A Randomized Study. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* **2003**, *14*, 140–143, doi:10.1034/J.1399-3038.2003.00021.X.
64. Garavello, W.; di Berardino, F.; Romagnoli, M.; Sambataro, G.; Gaini, R.M. Nasal Rinsing with Hypertonic Solution: An Adjunctive Treatment for Pediatric Seasonal Allergic Rhinoconjunctivitis. *International archives of allergy and immunology* **2005**, *137*, 310–314, doi:10.1159/000086462.
65. Garavello, W.; Somigliana, E.; Acaia, B.; Gaini, L.; Pignataro, L.; Gaini, R.M. Nasal Lavage in Pregnant Women with Seasonal Allergic Rhinitis: A Randomized Study. *International archives of allergy and immunology* **2010**, *151*, 137–141, doi:10.1159/000236003.
66. Li, H.; Sha, Q.; Zuo, K.; Jiang, H.; Cheng, L.; Shi, J.; Xu, G. Nasal Saline Irrigation Facilitates Control of Allergic Rhinitis by Topical Steroid in Children. *ORL; journal for oto-rhino-laryngology and its related specialties* **2009**, *71*, 50–55, doi:10.1159/000178165.
67. Nguyen, S.A.; Psaltis, A.J.; Schlosser, R.J. Isotonic Saline Nasal Irrigation Is an Effective Adjunctive Therapy to Intranasal Corticosteroid Spray in Allergic Rhinitis. *American journal of rhinology & allergy* **2014**, *28*, 308–311, doi:10.2500/AJRA.2014.28.4066.
68. Chkhartishvili, E.; Zhorzholiani, L.; Karseladze, R. Nasal Disease Management by Using Aqua Maris Solution. *Ann Biomed Res Edu* **2004**, *4*, 186–187.
69. Kim, C.H.; Hyun Song, M.; Eun Ahn, Y.; Lee, J.G.; Yoon, J.H. Effect of Hypo-, Iso- and Hypertonic Saline Irrigation on Secretory Mucins and Morphology of Cultured Human Nasal Epithelial Cells. *Acta oto-laryngologica* **2005**, *125*, 1296–1300, doi:10.1080/00016480510012381.
70. Wormald, P.J.; Cain, T.; Oates, L.; Hawke, L.; Wong, I. A Comparative Study of Three Methods of Nasal Irrigation. *The Laryngoscope* **2004**, *114*, 2224–2227, doi:10.1097/01.MLG.0000149463.95950.C5.

71. Bachmann, G.; Hommel, G.; Michel, O. Effect of Irrigation of the Nose with Isotonic Salt Solution on Adult Patients with Chronic Paranasal Sinus Disease. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* **2000**, *257*, 537–541, doi:10.1007/S004050000271.
72. Rabone, S.J.; Saraswati, S.B. Acceptance and Effects of Nasal Lavage in Volunteer Woodworkers. *Occupational medicine (Oxford, England)* **1999**, *49*, 365–369, doi:10.1093/OCCMED/49.6.365.
73. Kuzik, B.A.; al Qadhi, S.A.; Kent, S.; Flavin, M.P.; Hopman, W.; Hotte, S.; Gander, S. Nebulized Hypertonic Saline in the Treatment of Viral Bronchiolitis in Infants. *The Journal of pediatrics* **2007**, *151*, doi:10.1016/J.JPEDS.2007.04.010.
74. Stobbelaar, K.; Kool, M.; de Kruijf, D.; van Hoorenbeeck, K.; Jorens, P.; de Dooy, J.; Verhulst, S. Nebulised Hypertonic Saline in Children with Bronchiolitis Admitted to the Paediatric Intensive Care Unit: A Retrospective Study. *Journal of paediatrics and child health* **2019**, *55*, 1125–1132, doi:10.1111/JPC.14371.
75. Wang, Y.H.; Ku, M.S.; Sun, H.L.; Lue, K.H. Efficacy of Nasal Irrigation in the Treatment of Acute Sinusitis in Atopic Children. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi* **2014**, *47*, 63–69, doi:10.1016/J.JMII.2012.08.018.
76. Köksal, T.; Çizmeci, M.N.; Bozkaya, D.; Kanburoğlu, M.K.; Şahin, Ş.; Taş, T.; Yüksel, Ç.N.; Tatli, M.M. Comparison between the Use of Saline and Seawater for Nasal Obstruction in Children under 2 Years of Age with Acute Upper Respiratory Infection. *Turkish journal of medical sciences* **2016**, *46*, 1004–1013, doi:10.3906/SAG-1507-18.
77. Bogomilskiy, M.R.; Radcig, E.; Radcig, A.N. Complex Treatment of Acute Infectious Rhinitis in Children. *Pediatrija. Žurnal IM. G.N. Speranskogo* **2019**, *98*, 120–123.
78. Karpova, E.P.; Feĭzullaev, E.F. Experience in Using Laryngeal Aqua Maris Spray for the Local Treatment of Chronic Tonsillitis in Children. *Vestnik otorinolaringologii* **2008**, *4*, 85–86.
79. Passàli, D.; Damiani, V.; Passàli, F.M.; Passàli, G.C.; Bellussi, L. Atomized Nasal Douche vs Nasal Lavage in Acute Viral Rhinitis. *Archives of otolaryngology--head & neck surgery* **2005**, *131*, 788–790, doi:10.1001/ARCHOTOL.131.9.788.
80. Ramalingam, S.; Graham, C.; Dove, J.; Morrice, L.; Sheikh, A. Hypertonic Saline Nasal Irrigation and Gargling Should Be Considered as a Treatment Option for COVID-19. *Journal of global health* **2020**, *10*, doi:10.7189/JOGH.10.010332.
81. Low, T.H.; Woods, C.M.; Ullah, S.; Carney, A.S. A Double-Blind Randomized Controlled Trial of Normal Saline, Lactated Ringer's, and Hypertonic Saline Nasal Irrigation Solution after Endoscopic Sinus Surgery. *American journal of rhinology & allergy* **2014**, *28*, 225–231, doi:10.2500/AJRA.2014.28.4031.
82. Rapiejko, P.; Jurkiewicz, D. [The Use of Hypertonic Sea-Water Solution in Patients after Surgery of the Nose and Paranasal Sinuses]. *Otolaryngologia polska = The Polish otolaryngology* **2010**, *64*, 20–30, doi:10.1016/S0030-6657(10)70031-7.
83. Marchisio, P.; Picca, M.; Torretta, S.; Baggi, E.; Pasinato, A.; Bianchini, S.; Nazzari, E.; Esposito, S.; Principi, N. Nasal Saline Irrigation in Preschool Children: A Survey of Attitudes and Prescribing Habits of Primary Care Pediatricians Working in Northern Italy. *Italian journal of pediatrics* **2014**, *40*, doi:10.1186/1824-7288-40-47.
84. Baxter, A.L.; Schwartz, K.R.; Johnson, R.W.; Kuchinski, A.-M.; Swartout, K.M.; Rao, A.S.R.S.; Gibson, R.W.; Cherian, E.; Giller, T.; Boomer, H.; et al. Rapid Initiation of Nasal Saline Irrigation to Reduce Severity in High-

Risk COVID+ Outpatients: A Randomized Clinical Trial Compared to a National Dataset Observational Arm. *medRxiv* **2021**, 2021.08.16.21262044, doi:10.1101/2021.08.16.21262044.

85. Farrell, N.F.; Klatt-Cromwell, C.; Schneider, J.S. Benefits and Safety of Nasal Saline Irrigations in a Pandemic-Washing COVID-19 Away. *JAMA otolaryngology-- head & neck surgery* **2020**, *146*, 787–788, doi:10.1001/JAMAOTO.2020.1622.
86. Casale, M.; Rinaldi, V.; Sabatino, L.; Moffa, A.; Ciccozzi, M. Could Nasal Irrigation and Oral Rinse Reduce the Risk for COVID-19 Infection? *International journal of immunopathology and pharmacology* **2020**, *34*, doi:10.1177/2058738420941757.
87. Panta, P.; Chatti, K.; Andhavarapu, A. Do Saline Water Gargling and Nasal Irrigation Confer Protection against COVID-19? *Explore (New York, N.Y.)* **2021**, *17*, 127–129, doi:10.1016/J.EXPLORE.2020.09.010.
88. Huijghebaert, S.; Hoste, L.; Vanham, G. Essentials in Saline Pharmacology for Nasal or Respiratory Hygiene in Times of COVID-19. *European journal of clinical pharmacology* **2021**, *77*, 1275–1293, doi:10.1007/S00228-021-03102-3.
89. Chatterjee, U.; Chakraborty, A.; Naskar, S.; Bandyapadhyay, B.; Shee, S. Efficacy of Normal Saline Nasal Spray and Gargle on SARS-CoV-2 for Prevention of COVID-19 Pneumonia. **2021**, doi:10.21203/RS.3.RS-153598/V1.
90. Singh, S.; Sharma, N.; Singh, U.; Singh, T.; Mangal, D.; Singh, V. Nasopharyngeal Wash in Preventing and Treating Upper Respiratory Tract Infections: Could It Prevent COVID-19? *Lung India : official organ of Indian Chest Society* **2020**, *37*, 246–251, doi:10.4103/LUNGINDIA.LUNGINDIA_241_20.
91. Taccariello, M.; Parikh, A.; Darby, Y.; Scadding, G. Nasal Douching as a Valuable Adjunct in the Management of Chronic Rhinosinusitis. *Rhinology* **1999**, *37*, 29–32.
92. Cordray, S.; Harjo, J.B.; Miner, L. Comparison of Intranasal Hypertonic Dead Sea Saline Spray and Intranasal Aqueous Triamcinolone Spray in Seasonal Allergic Rhinitis. *Ear, Nose and Throat Journal* **2005**, *84*, 426–430, doi:10.1177/014556130508400713.
93. Ural, A.; Oktemer, T.K.; Kizil, Y.; Ileri, F.; Uslu, S. Impact of Isotonic and Hypertonic Saline Solutions on Mucociliary Activity in Various Nasal Pathologies: Clinical Study. *The Journal of laryngology and otology* **2009**, *123*, 517–521, doi:10.1017/S0022215108003964.
94. Gelardi, M.; Fiorella, M.L.; Gioacchino, M. di; Ciprandi, G. *IMMUNE EFFECTS OF NICKEL View Project ARIA Italy (Allergic Rhinitis and Its Impact on Asthma) View Project*; 2009;
95. Satdhabudha, A.; Poachanukoon, O. Efficacy of Buffered Hypertonic Saline Nasal Irrigation in Children with Symptomatic Allergic Rhinitis: A Randomized Double-Blind Study. *International journal of pediatric otorhinolaryngology* **2012**, *76*, 583–588, doi:10.1016/J.IJPORL.2012.01.022.
96. Stoelzel, K.; Bothe, G.; Chong, P.W.; Lenarz, M. Safety and Efficacy of Nasya/Prevalin in Reducing Symptoms of Allergic Rhinitis. *The clinical respiratory journal* **2014**, *8*, 382–390, doi:10.1111/CRJ.12080.
97. Alvarez-Puebla, M.J.; Olaguibel, J.M.; Almudevar, E.; Echegoyen, A.A.; Vela, C.; de Esteban, B. Mannitol versus Hypertonic Saline: Safety and Efficacy of Mannitol and Hypertonic Saline in Sputum Induction and Bronchial Hyperreactivity Assessment. *Chronic respiratory disease* **2015**, *12*, 197–203, doi:10.1177/1479972315576144.
98. Craig, S.S.; Seith, R.W.; Cheek, J.A.; Wilson, K.; Egerton-Warburton, D.; Paul, E.; West, A. Lidocaine and Phenylephrine versus Saline Placebo Nasal Spray for the Pain and Distress of Nasogastric Tube Insertion in Young Children and Infants: A Randomised, Double-Blind, Controlled Trial. *The Lancet. Child & adolescent health* **2019**, *3*, 391–397, doi:10.1016/S2352-4642(19)30058-6.

99. Huang, S.; Constant, S.; de Servi, B.; Meloni, M.; Saaid, A.; Culig, J.; Bertini, M. Is a Diluted Seawater-Based Solution Safe and Effective on Human Nasal Epithelium? *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* **2021**, *278*, 2837–2842, doi:10.1007/S00405-020-06527-1.
100. Jiang, M.; Chen, J.; Ding, Y.; Gan, C.; Hou, Y.; Lei, J.; Wan, M.; Li, X.; Xiao, Z. Efficacy and Safety of Sea Salt-Derived Physiological Saline Nasal Spray as Add-On Therapy in Patients with Acute Upper Respiratory Infection: A Multicenter Retrospective Cohort Study. *Medical science monitor : international medical journal of experimental and clinical research* **2021**, *27*, doi:10.12659/MSM.929714.
101. Papsin, B.; McTavish, A. Saline Nasal Irrigation: Its Role as an Adjunct Treatment. *Canadian Family Physician* **2003**, *49*, 168.
102. Brown, C.L.; Graham, S.M. Nasal Irrigations: Good or Bad? *Current opinion in otolaryngology & head and neck surgery* **2004**, *12*, 9–13, doi:10.1097/00020840-200402000-00004.
103. Harvey, R.; Hannan, S.A.; Badia, L.; Scadding, G. Nasal Saline Irrigations for the Symptoms of Chronic Rhinosinusitis. *The Cochrane database of systematic reviews* **2007**, doi:10.1002/14651858.CD006394.PUB2.
104. Kassel, J.C.; King, D.; Spurling, G.K. Saline Nasal Irrigation for Acute Upper Respiratory Tract Infections. *The Cochrane database of systematic reviews* **2010**, doi:10.1002/14651858.CD006821.PUB2.
105. Zhang, L.; Mendoza-Sassi, R.A.; Wainwright, C.; Klassen, T.P. Nebulized Hypertonic Saline Solution for Acute Bronchiolitis in Infants. *Cochrane Database of Systematic Reviews* **2008**, doi:10.1002/14651858.CD006458.PUB2/INFORMATION/EN.
106. Adappa, N.D.; Wei, C.C.; Palmer, J.N. Nasal Irrigation with or without Drugs: The Evidence. *Current opinion in otolaryngology & head and neck surgery* **2012**, *20*, 53–57, doi:10.1097/MOO.0B013E32834DFA80.
107. Chirico, G.; Quartarone, G.; Mallefet, P. Nasal Congestion in Infants and Children: A Literature Review on Efficacy and Safety of Non-Pharmacological Treatments. *Minerva Pediatrica* **2014**, *66*, 549–557.
108. Madison, S.; Brown, E.A.; Franklin, R.; Wickersham, E.A.; McCarthy, L.H. Nasal Saline or Intranasal Corticosteroids to Treat Allergic rhinitis in Children. *The Journal of the Oklahoma State Medical Association* **2016**, *109*, 152.
109. Kanjanawasee, D.; Seresirikachorn, K.; Chitsuthipakorn, W.; Snidvongs, K. Hypertonic Saline Versus Isotonic Saline Nasal Irrigation: Systematic Review and Meta-Analysis. *American journal of rhinology & allergy* **2018**, *32*, 269–279, doi:10.1177/1945892418773566.
110. Li, C.L.; Lin, H.C.; Lin, C.Y.; Hsu, T.F. Effectiveness of Hypertonic Saline Nasal Irrigation for Alleviating Allergic Rhinitis in Children: A Systematic Review and Meta-Analysis. *Journal of clinical medicine* **2019**, *8*, doi:10.3390/JCM8010064.
111. King, D. What Role for Saline Nasal Irrigation? *Drug and therapeutics bulletin* **2019**, *57*, 56–59, doi:10.1136/DTB.2018.000023.