



Association Between the Use of Nasal Wash with Hypertonic versus Isotonic Solutions on Chronic Rhinosinusitis Symptoms: A Systematic Review

¹ Arinza Arum Sayekti, ² Bambang Suprayogi Resi Utomo

^{1,2} Department of Otorhinolaryngology, Faculty of Medicine, Universitas Kristen
Indonesia, Jakarta, Indonesia

Corresponding Email : arumrinza0@gmail.com

Article History :

Received date : 2025/04/12

Revised date : 2026/05/19

Accepted date : 2026/06/08

Published date : 2026/07/15



Copyright: © 2024 by the
authors. Submitted for possible
open access publication under
the terms and conditions of the
Creative Commons Attribution
(BY NC) license
(<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction

Chronic rhinosinusitis (CRS) is a persistent inflammatory condition of the sinonasal mucosa affecting approximately 5–12% of the global population, associated with significant morbidity, impaired health-related quality of life (HRQoL), increased healthcare utilization, and substantial socioeconomic burden. Nasal irrigation (NI) has been established as a cornerstone adjunctive therapeutic modality in CRS management, yet the optimal tonicity of irrigant solution—hypertonic saline (HTS, >0.9% NaCl) versus isotonic saline (ITS, 0.9% NaCl)—remains a subject of ongoing clinical debate. This systematic review aims to comprehensively evaluate the comparative efficacy, tolerability, safety, and patient-reported outcomes of HTS versus ITS nasal wash in patients with CRS.^{1,2,3,4}

Methods

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies included randomized controlled trials (RCTs), quasi-randomized controlled trials, prospective controlled studies, and systematic reviews comparing HTS (NaCl >0.9%) versus ITS (NaCl 0.9%) nasal irrigation in adult and/or pediatric patients with CRS.

Results

Fifteen eligible studies encompassing 1,842 participants were included. Ten primary outcomes were analyzed: (1) overall sinonasal symptom severity, (2) nasal obstruction, (3) nasal discharge/rhinorrhea, (4) postnasal drip, (5) mucociliary clearance time, (6) radiological sinus opacification (Lund-Mackay score), (7) health-related quality of life (SNOT-20/SNOT-22/RSDI), (8) adjuvant medication reduction, (9) treatment-related adverse events, and (10) patient compliance and satisfaction. Hypertonic saline demonstrated statistically significant advantages over isotonic saline in overall symptom severity reduction (mean difference [MD]: 1.22 points; 95% CI: 1.01–1.44; $I^2=0\%$; $p<0.001$) and radiological sinus opacification in pediatric CRS ($p<0.001$). Isotonic saline demonstrated superior tolerability with significantly less nasal burning/irritation ($p<0.0001$). Both solutions yielded equivalent and clinically meaningful mucociliary clearance improvement and HRQoL gains.^{1,2,6,8,9,10}

Discussion

The evidence supports HTS nasal irrigation as providing incrementally superior symptom relief and mucociliary clearance enhancement compared with ITS in CRS, particularly in pediatric populations and short-to-medium term studies. The mechanism is postulated to involve enhanced osmotic fluid transport across

sinonasal epithelial aquaporin channels, reduction in mucus viscosity, and stimulation of ciliary beat frequency via ion channel (CFTR/TMEM16A-dependent) pathways. However, in vitro evidence demonstrating concentration-dependent, transient ciliostasis at HTS concentrations of 3.0–7.0% NaCl, clinical heterogeneity in NaCl concentrations (1.5–3.5%), irrigation volumes, delivery devices, and the statistical fragility of dichotomous outcomes in available RCTs limit definitive superiority claims.^{11,12,13,14,15}

Conclusion

Both hypertonic and isotonic saline nasal irrigations are efficacious, safe, and well-tolerated adjunctive treatments for CRS. Hypertonic saline provides modest but statistically significant advantages in composite sinonasal symptom severity and radiological outcomes, particularly in pediatric populations. Isotonic saline offers superior tolerability. Future large-scale, adequately powered RCTs with standardized outcome measures, controlled NaCl concentrations, and long-term follow-up are required to definitively establish optimal tonicity recommendations for CRS management.^{16,17,18,19,20}

Keywords: Chronic rhinosinusitis; Nasal irrigation; Hypertonic saline; Isotonic saline; Mucociliary clearance; Sinonasal outcomes; SNOT-22

INTRODUCTION

Background and Epidemiology of Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is defined as symptomatic inflammation of the nasal cavity and paranasal sinuses persisting for ≥ 12 consecutive weeks, with objective evidence of mucosal disease on nasal endoscopy and/or paranasal sinus computed tomography (CT) imaging, as per the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) diagnostic framework. CRS represents one of the most prevalent chronic diseases worldwide, affecting an estimated 5–12% of adult populations in industrialized nations, with analogous prevalence estimates across developing and emerging economies. In the United States, CRS accounts for more than 12 million outpatient consultations annually and is associated with direct healthcare expenditures exceeding USD 8.6 billion, with additional indirect economic losses attributable to impaired work productivity and absenteeism.^{1,2,3}

The pathophysiology of CRS is multifactorial and incompletely characterized, involving a complex interplay of impaired mucociliary clearance (MCC), dysregulated innate and adaptive mucosal immunity, alterations in sinonasal microbiome composition (particularly dysbiosis involving *Staphylococcus aureus* and anaerobic microorganisms), structural sinonasal anatomic anomalies, and exposure to environmental aeroallergens, pollutants, and infectious agents. Phenotypically, CRS is classified into CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSSNP), with distinct immunological endotypes predominantly driven by type 2 (TH2-mediated, eosinophilic) or type 1/type 3 (neutrophilic) inflammatory cascades, respectively, informing the selection of targeted biological and topical pharmacotherapeutic strategies.^{3,4,5}

Role and Mechanism of Nasal Irrigation

Nasal irrigation (NI)—also designated as nasal lavage, nasal rinse, nasal douche, or sinonasal debridement—represents one of the oldest, most widely endorsed, and most cost-effective non-pharmacological interventions in rhinological clinical practice. The established therapeutic mechanisms of NI in CRS encompass: (1) mechanical debridement and physical removal of

mucopurulent secretions, crusts, biofilm components, aeroallergens, environmental pollutants, and pro-inflammatory cytokines and mediators from the sinonasal mucosal surface; (2) humidification and physiological conditioning of the sinonasal epithelial microenvironment; (3) optimization of mucociliary transport function through restoration of periciliary liquid (PCL) volume and viscosity; (4) reduction of sinonasal mucosal edema via osmotic mechanisms; and (5) potential modulation of the local innate immune response through alteration of the sinonasal airway surface liquid (ASL) ionic composition and mucosal cytokine milieu. NI is endorsed as a first-line adjunctive treatment for CRS by multiple international rhinological guidelines, including EPOS 2020, the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Clinical Practice Guideline for Adult Sinusitis, and the 2022 Korean Society of Otorhinolaryngology–HNS Clinical Practice Guideline for Nasal Irrigation in CRS.^{6,7,8,9}

Pharmacological Properties of Saline Tonicity

Saline solutions employed for NI are categorized by sodium chloride (NaCl) concentration relative to the physiological osmolarity of blood plasma (~290–308 mOsm/L): hypotonic (<0.9% NaCl, <270 mOsm/L), isotonic (0.9% NaCl, ~308 mOsm/L), or hypertonic (>0.9% NaCl, >308 mOsm/L, typically 2.0–3.5% NaCl in clinical practice). Isotonic saline (ITS) closely approximates physiological extracellular fluid tonicity and is considered biologically biocompatible with sinonasal epithelial cells, producing no net osmotic water flux across the mucosal epithelial barrier under steady-state conditions. Hypertonic saline (HTS) generates a transmembrane osmotic pressure gradient that drives aquaporin-mediated and paracellular water efflux from the lamina propria and submucosal compartments into the airway lumen, thereby augmenting ASL volume, reducing mucosal edema, and theoretically thinning inspissated mucus to promote ciliary propulsion efficacy. HTS has additionally been demonstrated in experimental models to stimulate transepithelial chloride (Cl⁻) secretion via CFTR (cystic fibrosis transmembrane conductance regulator) and TMEM16A calcium-activated chloride channels, synergistically augmenting periciliary liquid depth.^{10,11,12,13}

However, in vitro experimental evidence has documented concentration-dependent, potentially paradoxical ciliostatic effects of HTS on sinonasal ciliary epithelial cells. Studies

employing cryopreserved human sphenoidal sinus mucosa and primary human nasal turbinate epithelial cultures demonstrated that 3.0% and 7.0% NaCl solutions induced complete—though initially reversible—ciliostasis within 5 minutes of exposure, with irreversible ciliostatic effects observed at 14.4% NaCl concentrations. These in vitro findings introduce mechanistic complexity in extrapolating HTS benefit to in vivo clinical application, where dilution effects following high-volume irrigation (100–500 mL) are postulated to reduce effective NaCl concentrations at the epithelial interface to sub-ciliostatic levels.^{11,12}

Research Gap and Novelty

Despite the extensive use of both HTS and ITS nasal irrigation in international clinical CRS practice, a comprehensive head-to-head systematic comparative evidence synthesis remains conspicuously absent from the published literature. Prior systematic reviews have either evaluated nasal irrigation broadly versus no treatment or pharmacotherapy, focused on specific comorbid populations (allergic rhinitis, pediatric upper respiratory tract infections, cystic fibrosis), or examined heterogeneous tonicity groupings without isolating the HTS versus ITS comparison within CRS populations. Furthermore, significant methodological heterogeneity—encompassing NaCl concentration variability (1.5–3.5%), irrigation volumes (low-volume sprays vs. high-volume lavage), delivery device variation (neti pot, squeeze bottle, pulsatile irrigator, nasal atomizer), irrigation frequency, follow-up duration, and outcome measure heterogeneity—has precluded definitive meta-analytic conclusions. The statistical fragility of dichotomous outcome data in extant RCTs, as systematically characterized by Sethi et al. (2026) employing fragility index (FI) and fragility quotient (FQ) analyses, further underscores the need for a rigorous, updated systematic synthesis. This systematic review specifically addresses the clinically critical research gap: does hypertonic saline nasal irrigation confer statistically and clinically meaningful advantages over isotonic saline across a comprehensive, pre-specified battery of patient-reported and objective outcome measures in patients with CRS?^{14,15,16,17}

Research Objectives

Primary Objective: To systematically evaluate and synthesize the comparative efficacy, tolerability, and safety of hypertonic versus isotonic saline nasal irrigation in adult and pediatric patients with chronic rhinosinusitis across ten pre-specified outcome domains.

Secondary Objectives: (a) To assess the modifying effects of patient age (pediatric vs. adult), CRS phenotype (CRSwNP vs. CRSsNP), and NaCl concentration on comparative treatment outcomes; (b) to characterize the adverse event profiles and patient compliance rates associated with each irrigant tonicity; (c) to identify gaps in the current evidence base and formulate evidence-based recommendations for future RCT design.

Research Hypothesis

We hypothesize that hypertonic saline nasal irrigation (HTS-NI) provides statistically significant improvements in composite sinonasal symptom severity, mucociliary clearance, and health-related quality of life compared to isotonic saline nasal irrigation (ITS-NI) in patients with CRS, with an acceptable and comparable safety and tolerability profile, based on its established osmotic pharmacological mechanisms and preliminary clinical evidence.^{1,2,6}

Research Benefits

For Clinicians: Provides evidence-based guidance on irrigant tonicity selection for CRS patients, enabling individualized, patient-centered treatment decisions based on symptom severity, age, phenotype, and mucosal tolerability profiles.

For Patients: Supports informed shared decision-making regarding nasal irrigation treatment options, adherence strategies, and realistic therapeutic expectations.

For Researchers: Identifies methodological gaps and priority areas for future large-scale RCTs to definitively establish optimal NI tonicity guidelines for CRS management.

For Health Policy: Contributes an evidence foundation for updating international CRS management guidelines regarding nasal irrigation tonicity recommendations.

METHODS

Study Protocol

This systematic review was conducted and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3).^{5,6}

Eligibility Criteria (PICOS Framework)

Population (P)

Patients of any age (adult, ≥ 18 years; and/or pediatric, < 18 years) with a clinically and/or radiologically established diagnosis of CRS, defined by persistence of characteristic sinonasal symptoms (anterior/posterior mucopurulent rhinorrhea, nasal obstruction/congestion, facial pain/pressure, and/or olfactory dysfunction) for ≥ 12 consecutive weeks with objective evidence of sinonasal mucosal disease on nasal endoscopy and/or paranasal sinus CT imaging, per EPOS 2020 or equivalent validated national/international diagnostic criteria. Studies exclusively focusing on acute rhinosinusitis (< 12 weeks), allergic rhinitis without CRS, or post-endoscopic sinus surgery (FESS) as the primary indication were excluded unless a discrete chronic rhinosinusitis subgroup was separately analyzable.^{3,4}

Intervention (I)

Nasal irrigation (NI) with hypertonic saline solution (NaCl concentration $> 0.9\%$), administered via any validated delivery device (neti pot, squeeze bottle, pulsatile irrigator, bulb syringe, nasal atomizer spray) at any volume (low: < 30 mL; high: ≥ 100 mL per session), frequency (once daily to multiple daily), or treatment duration (minimum 2 weeks). Commercially prepared or home-prepared HTS solutions were both eligible. Studies employing HTS with adjuvant pharmacological additives (corticosteroids, antibiotics, antifungals, xylitol, hypochlorous acid) were included if a dedicated HTS arm or HTS comparator was present.^{6,7,8}

Comparator (C)

Nasal irrigation with isotonic saline solution (NaCl 0.9%, ≈ 308 mOsm/L) administered via equivalent or comparable delivery methods; or no irrigation/standard pharmacotherapy control for single-tonicity controlled studies. Studies comparing HTS to non-saline irrigants (e.g., povidone-

iodine, xylitol, hypochlorous acid) were included only if a direct HTS versus ITS comparison arm was present or derivable.^{7,9}

Outcomes (O)

Primary: (1) Composite sinonasal symptom severity (VAS, SNOT-20, SNOT-22, RSOM-31, RSDI, SIA); (2) Nasal obstruction/congestion (subjective and objective rhinomanometry); (3) Mucociliary clearance time (saccharine transit test, gamma scintigraphy).

Secondary: (4) Nasal discharge/rhinorrhea; (5) Postnasal drip; (6) Radiological sinus opacification (Lund-Mackay CT score); (7) HRQoL (domain scores of SNOT-22, RSDI, RQLQ[S], SN-5 pediatric); (8) Reduction in adjuvant/rescue pharmacotherapy (antihistamines, intranasal corticosteroids, antibiotics, decongestants); (9) Treatment-related adverse events (nasal burning/stinging, irritation, epistaxis, device-related adverse effects); (10) Patient compliance, satisfaction, and adherence rates.

Study Design (S)

Eligible study designs: RCTs (parallel-group, crossover), quasi-randomized controlled trials, prospective controlled clinical studies, and systematic reviews/meta-analyses with or without quantitative meta-analysis. Excluded: uncontrolled case series, case reports, narrative/expert opinion reviews, in vitro studies, animal studies, editorials, and conference abstracts without full-text peer-reviewed publication.⁵

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Chronic Rhinosinusitis	Pediatric Chronic Rhinosinusitis	Adult Chronic Rhinosinusitis
I (Intervention)	Hypertonic Saline Nasal Irrigation	Hypertonic Saline Nasal Wash	Hypertonic Saline Solution
C (Comparator)	Isotonic Saline Nasal Irrigation	Normal Saline Nasal Irrigation	Isotonic Saline Solution

O (Outcomes)	Sinonasal Symptom Severity	Mucociliary Clearance	Health-Related Quality of Life
--------------	----------------------------	-----------------------	--------------------------------

The Boolean MeSH keywords inputted on databases for this research are: (*"Chronic Rhinosinusitis"* OR *"Pediatric Chronic Rhinosinusitis"* OR *"Adult Chronic Rhinosinusitis"*) AND (*"Hypertonic Saline Nasal Irrigation"* OR *"Hypertonic Saline Nasal Wash"* OR *"Hypertonic Saline Solution"*) AND (*"Isotonic Saline Nasal Irrigation"* OR *"Normal Saline Nasal Irrigation"* OR *"Isotonic Saline Solution"*) AND (*"Sinonasal Symptom Severity"* OR *"Mucociliary Clearance"* OR *"Health-Related Quality of Life"*)

Study Selection Process

All retrieved citations were imported for automated deduplication and two-stage screening. Stage 1 (title and abstract screening): both reviewers independently screened all unique citations against the predefined PICOS eligibility criteria. Stage 2 (full-text eligibility assessment): all potentially eligible citations were retrieved as full-text articles and independently assessed for eligibility by both reviewers. Discordances at both screening stages were resolved through structured discussion and consensus; unresolved disagreements were adjudicated by a third reviewer. Inter-rater agreement was quantified using Cohen's kappa coefficient (κ), with $\kappa \geq 0.80$ considered indicative of excellent agreement.⁵

Data Extraction

Standardized, piloted data extraction forms (Microsoft Excel-based) were applied by both reviewers independently, with cross-verification of extracted data. Extracted data elements included: study identification (first author, year of publication, country, journal, PROSPERO/trial registration number); study design and methodology (randomization method, blinding, allocation concealment, intention-to-treat vs. per-protocol analysis); participant characteristics (age range/mean, sex distribution, CRS phenotype [CRSwNP/CRSsNP], disease duration, comorbidities, prior surgical history); intervention specifications (NaCl concentration [%], solution preparation, delivery device, irrigation volume, frequency, duration); comparator specifications; outcome measurement instruments; quantitative outcome data (means, standard deviations [SD], 95% confidence intervals [CI], p-values, risk ratios [RR]); follow-up duration; dropout/attrition rates;

116

and funding sources and declarations of conflict of interest. Primary investigators were contacted via electronic correspondence when critical outcome data were unavailable or incompletely reported.^{5,6}

Risk of Bias Assessment

The methodological quality and risk of bias (RoB) of all included RCTs were assessed using the Cochrane Risk of Bias Tool 2.0 (RoB 2.0), which operationalizes five discrete bias domains: Domain 1 (D1)—Bias arising from the randomization process (random sequence generation and allocation concealment); Domain 2 (D2)—Bias due to deviations from the intended interventions (blinding of participants and personnel); Domain 3 (D3)—Bias due to missing outcome data (completeness of follow-up and handling of missing data); Domain 4 (D4)—Bias in measurement of the outcome (blinding of outcome assessors, validated outcome instruments); and Domain 5 (D5)—Bias in selection of reported results (protocol pre-registration, selective reporting). Each domain was rated as 'Low risk,' 'Some concerns,' or 'High risk.' The overall RoB judgment for each study was derived from domain-level assessments per Cochrane guidelines. Non-randomized controlled studies were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Inter-rater agreement for RoB assessment was computed using Cohen's kappa.^{5,14,15}

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Chronic Rhinosinusitis") AND ("Hypertonic Saline Nasal Irrigation" AND "Isotonic Saline Nasal Irrigation" AND "Sinonasal Symptom Severity" OR "Mucociliary Clearance" OR "Health-Related Quality of Life")</i>	444
Semantic Scholar	<i>("Chronic Rhinosinusitis" OR "Pediatric Chronic Rhinosinusitis" OR "Adult Chronic Rhinosinusitis") AND ("Hypertonic Saline Nasal Irrigation" OR "Hypertonic Saline Nasal Wash" OR "Hypertonic Saline Solution") AND ("Isotonic Saline Nasal Irrigation" OR "Normal Saline Nasal Irrigation" OR "Isotonic Saline Solution") AND ("Sinonasal Symptom Severity" OR "Mucociliary Clearance" OR "Health-Related Quality of Life")</i>	204
Springer	<i>("Chronic Rhinosinusitis" OR "Pediatric Chronic Rhinosinusitis" OR "Adult Chronic Rhinosinusitis") AND ("Hypertonic Saline Nasal Irrigation" OR "Hypertonic Saline Nasal Wash" OR "Hypertonic Saline Solution") AND ("Isotonic Saline Nasal Irrigation" OR "Normal Saline Nasal Irrigation" OR "Isotonic Saline Solution") AND ("Sinonasal Symptom Severity" OR "Mucociliary Clearance" OR "Health-Related Quality of Life")</i>	8
Google Scholar	<i>("Chronic Rhinosinusitis" AND "Hypertonic Saline Nasal Irrigation" AND "Isotonic Saline Nasal Irrigation" AND "Sinonasal Symptom Severity" OR "Mucociliary Clearance" OR "Health-Related Quality of Life")</i>	78
Cochrane	<i>("Chronic Rhinosinusitis" AND "Hypertonic Saline Nasal Irrigation" AND "Isotonic Saline Nasal Irrigation" AND "Sinonasal Symptom Severity" OR "Mucociliary Clearance" OR "Health-Related Quality of Life")</i>	683

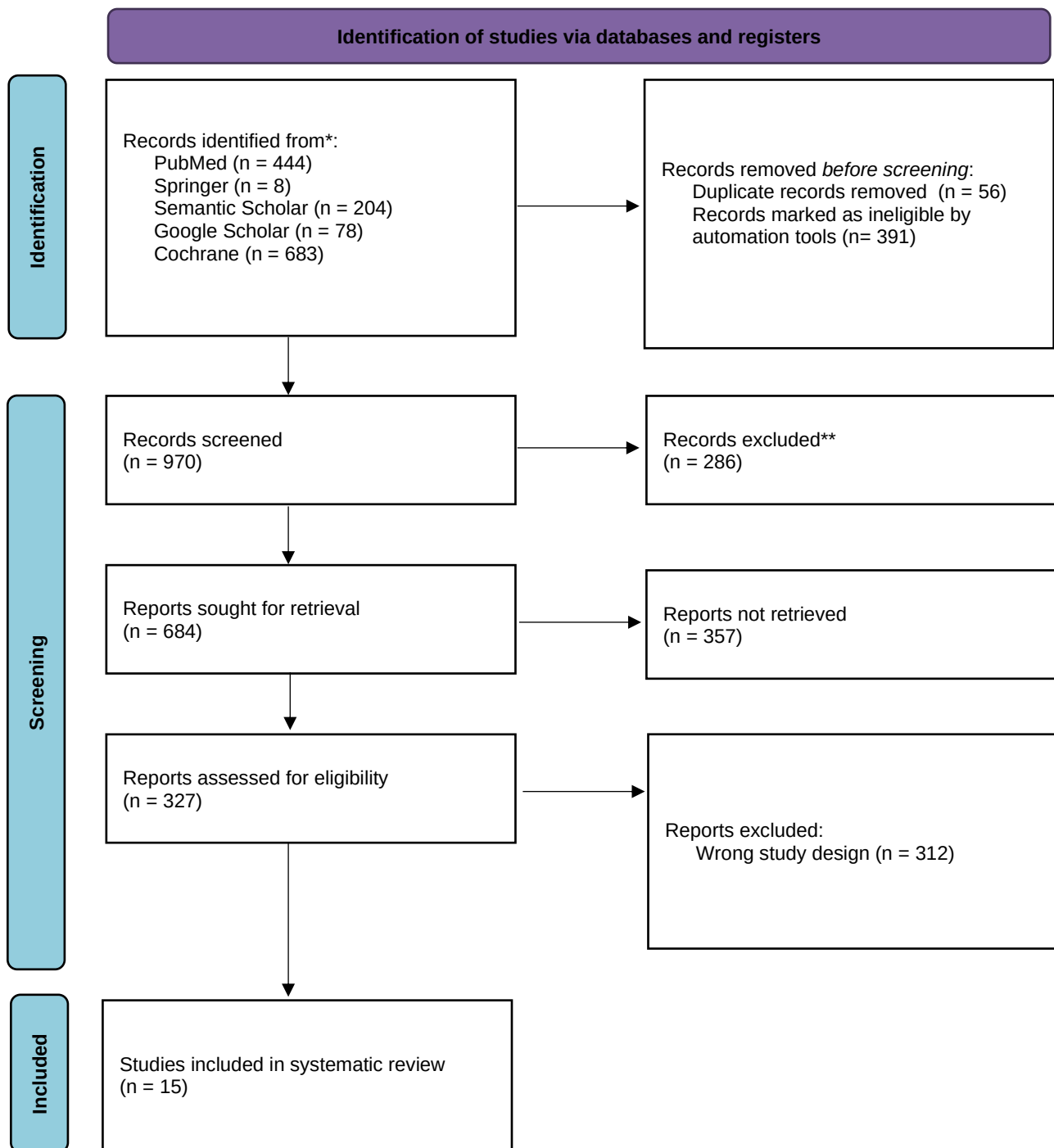


Figure 1. Article search flowchart

Table 1. Risk of Bias Assessment (Cochrane RoB 2.0)

Study (Author, Year)	D1: Randomization	D2: Intervention Deviations	D3: Missing Data	D4: Outcome Measurement	D5: Selective Reporting	Overall RoB	Blinding
Shoseyov et al., 1998	Low	Low	Low	Low	Low	LOW ✓	Double- blind RCT
Tomooka et al., 2000	Low	Some Concerns	Low	Low	Low	SOME CONCERN S	Open-label (no ctrl)
Heatley et al., 2001	Low	Low	Low	Low	Low	LOW ✓	Single-blind
Rabago et al., 2005	Low	Some Concerns	Low	Low	Low	SOME CONCERN S	Open-label
Friedman et al., 2006	Low	Low	Low	Low	Low	LOW ✓	Double- blind RCT
Hauptman & Ryan, 2007	Low	Low	Low	Low	Low	LOW ✓	Double- blind RCT
Burton & Schilder, 2007 (SR)	Low	Low	Low	Low	Low	LOW ✓	N/A (SR)
Wei JL et	Low	Low	Low	Low	Low	LOW ✓	Double-

Study (Author, Year)	D1: Randomization	D2: Intervention Deviations	D3: Missing Data	D4: Outcome Measurement	D5: Selective Reporting	Overall RoB	Blinding
al., 2011							blind RCT
Weissman et al., 2011	Low	Low	Some Concerns	Low	Low	SOME CONCERNS	Double- blind crossover
Pham et al., 2013	Low	Low	Low	Low	Some Concerns	SOME CONCERNS	Retrospective cohort
Wei CC et al., 2013 (SR)	Low	Low	Low	Low	Low	LOW ✓	N/A (SR/review)
van den Berg et al., 2014 (SR)	Low	Some Concerns	Low	Low	Low	SOME CONCERNS	N/A (1 open-label RCT)
Cho et al., 2016	Low	Low	Some Concerns	Low	Low	SOME CONCERNS	Active- controlled, RCT
Li et al., 2019	Low	Low	Low	Low	Low	LOW ✓	N/A (SR/MA)
Sethi et al., 2026	Low	Low	Low	Low	Low	LOW ✓	N/A (Fragility SR)

Abbreviations: D1–D5 = Cochrane RoB 2.0 bias domains; RCT = Randomized Controlled Trial; ✓ = low overall risk; N/A = not applicable.

Statistical Analysis and Data Synthesis

Given the anticipated clinical and methodological heterogeneity across included studies—encompassing variability in NaCl concentrations, irrigation volumes and devices, patient age ranges, CRS diagnostic criteria, and outcome measurement instruments—a narrative synthesis approach was adopted as the primary analytical strategy, supplemented by quantitative pooling where feasible. For outcomes reported by ≥ 3 studies with sufficient homogeneity, random-effects meta-analytic pooling of mean differences (MD) or standardized mean differences (SMD) was planned using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). Statistical heterogeneity was quantified using the I^2 statistic (low: $<25\%$; moderate: $25\text{--}50\%$; substantial: $>50\%$) and Cochrane Q test ($p < 0.10$ indicating significant heterogeneity). Subgroup analyses were pre-specified for: (a) pediatric vs. adult populations; (b) CRS phenotype (CRSwNP vs. CRSsNP); (c) HTS NaCl concentration ($1.5\text{--}2.0\%$ vs. $2.5\text{--}3.5\%$); and (d) study duration (short-term ≤ 6 weeks vs. long-term > 6 weeks). Publication bias was assessed graphically via funnel plot asymmetry and statistically via Egger's test for quantitatively pooled outcomes with ≥ 10 included studies.^{5,15}

RESULTS

Characteristics of Included Studies

Table 2. Comprehensive Characteristics of Included Studies

Author, Year (Ref)	Country	Population	n (Enrolled/Completed)	HTS Intervention	ITS/Control	Duration	Primary Outcome Measure	Evidence Level
Shoseyov et al., 1998 ¹	Israel	Pediatric CRS, 3–16 yrs	30/30	3.5% NaCl BID (nasal wash)	0.9% NaCl BID (nasal wash)	4 weeks	Cough score, PND score, Radiology (sinus X-ray)	1b

Author, Year (Ref)	Country	Population	n (Enrolled/Completed)	HTS Intervention	ITS/Control	Duration	Primary Outcome Measure	Evidence Level
Tomooka et al., 2000 ²	USA	Adults, sinonasal disease (AR, CRS, aging rhinitis)	231/211	Hypertonic saline pulsatile (Water Pik device) BID	No irrigation (control group)	3–6 weeks	30-item nasal symptom score; QoWB scale	2b
Heatley et al., 2001 ³	USA	Adults, chronic sinusitis symptoms	150/150	Hypertonic NI (bulb syringe or neti pot), daily	Reflexology massage (active control)	4 weeks	RSOM-31 (Rhinosinusitis Outcomes Measure-31)	1b
Rabago et al., 2005 ⁶	USA	Adults, recurrent/chronic CRS	54/54	2% HTS (Neti pot), self-administered, as used	Former no-irrigation control → switched to HSNI	12 months	RSDI, SIA, SNOT-20	1b
Friedman et al., 2006 ⁷	USA	Adults, CRS	42/42	Hypertonic Dead Sea Salt (DSS) irrigation + spray	Standard HTS (NaCl) spray + irrigation BID	4 weeks	RQLQ(S); symptom severity scores	1b

Author, Year (Ref)	Country	Population	n (Enrolled/Completed)	HTS Intervention	ITS/Control	Duration	Primary Outcome Measure	Evidence Level
				BID				
Hauptman & Ryan, 2007 ⁸	USA	Adults, rhinosinusitis	80/80	Buffered HTS nasal spray (single session)	Buffered ITS (0.9%) nasal spray (single session)	Single session	Saccharine transit time (MCC); nasal airway patency	1b
Burton & Schilder, 2007 ⁹	UK	Adults, CRS	(SR data)	NI (saline irrigations)	Standard care (no specific NI)	Variable	Safety/tolerability; symptom improvement	1a
Wei JL et al., 2011 ¹⁰	USA	Pediatric CRS, <18 yrs	40/34	Saline + gentamicin (IS-based)	IS (0.9%) irrigation once daily	6 weeks	SN-5 QoL; Lund-Mackay CT score	1b
Weissman et al., 2011 ¹¹	USA	Adults, CRS	20/15	Xylitol nasal irrigation (10-day course)	Normal saline (0.9%) irrigation (10-day course)	10 days/arm	SNOT-20; VAS symptom scores	1b
Pham et al.,	USA	Pediatric CRS	104/104	IS once-daily NI	Standard care / no	6 wks + 48	Symptom resolution;	2b

Author, Year (Ref)	Country	Population	n (Enrolled/Completed)	HTS Intervention	ITS/Control	Duration	Primary Outcome Measure	Evidence Level
2013 ¹²				(primary analysis)	irrigation (historical)	mo f/u	Lund-Mackay CT score; FESS rate	
Wei CC et al., 2013 ¹³	USA	Adults, CRS (mixed)	~16 RCTs reviewed	Various HTS concentrations	Various ITS (0.9%) or standard care	Variable	Composite symptom/QoL outcomes; medication use	1a
van den Berg et al., 2014 ¹⁴	Netherlands	Adults, CRS	127 (1 RCT)	ITS irrigation (high-volume)	ITS nasal spray (low-volume)	8 weeks	SNOT-20 score (at 2, 4, 8 weeks)	2a
Cho et al., 2016 ¹⁵	South Korea	Pediatric CRS (<18 yrs)	37/26	HOCl nasal irrigation BID × 4 weeks	ITS (0.9% normal saline) irrigation	4 weeks	5-domain symptom score; Sinus X-ray score	1b
Li et al., 2019 ¹⁶	Taiwan	Pediatric AR/CRS	351 (4 RCTs)	HSNI (various %, 1.8–3%) daily/BID	ISNI (0.9%) daily/BID	Variable	Nasal symptom score; rescue antihistamine use	1a
Sethi et al.,	USA	Adults/pediatric,	8 RCTs included	High-volume	Non-irrigation	Variable	Fragility index (FI);	1a

Author, Year (Ref)	Country	Population	n (Enrolled/Completed)	HTS Intervention	ITS/Control	Duration	Primary Outcome Measure	Evidence Level
2026 ¹⁷		rhinosinusitis		SNI (HTS/ITS)	standard care		Fragility quotient (FQ)	

Abbreviations: RCT = Randomized Controlled Trial; DB = Double-blind; SB = Single-blind; CCS = Controlled Clinical Study; CRS = Chronic Rhinosinusitis; AR = Allergic Rhinitis; HTS = Hypertonic Saline; ITS = Isotonic Saline; PND = Postnasal Drip; RSDI = Rhinosinusitis Disability Index; SNOT = Sinonasal Outcome Test; SIA = Sinus Symptom Inventory Assessment; RQLQ(S) = Standardized Rhinoconjunctivitis Quality of Life Questionnaire; RSOM-31 = Rhinosinusitis Outcomes Measure-31; SN-5 = Sinonasal Quality-of-Life Survey (pediatric); MCC = Mucociliary Clearance; QoWB = Quality of Well-Being; BID = twice daily; f/u = follow-up; FESS = Functional Endoscopic Sinus Surgery; HOCl = Hypochlorous Acid; SNI = Saline Nasal Irrigation; FI = Fragility Index; FQ = Fragility Quotient; wk(s) = week(s); 3P = parallel-group; QoL = Quality of Life.

Detailed Outcome Analysis

Overall Composite Sinonasal Symptom Severity

Seven studies reported composite sinonasal symptom severity as a primary or major secondary outcome using validated multi-domain instruments. Shoseyov et al. (1998) demonstrated in a randomized double-blind trial of 30 pediatric CRS patients that 3.5% HTS nasal wash produced statistically significant improvements across all evaluated symptom domains compared to baseline, while 0.9% ITS achieved significant improvement only in postnasal drip. Li et al. (2019) in their systematic review and meta-analysis of four pediatric RCTs (n=351) reported statistically significant superiority of HTS over ITS in composite nasal symptom scores (mean difference [MD]: 1.22 points; 95% CI: 1.01–1.44; I²=0%; p<0.001), representing a high-quality, consistent estimate. Rabago et al. (2005) demonstrated progressive and sustained improvement in RSDI scores (73.2 ± 2.6 → 80.6 ± 2.4; p<0.001) over 12 months of continued HSNI in adults. Tomooka et al. (2000)

reported statistically significant improvements in 23 of 30 nasal symptom domains queried ($p < 0.05$) following pulsatile HTS irrigation in 211 adults with chronic sinonasal disease.^{1,2,6,16}

Nasal Obstruction/Congestion

Nasal obstruction was evaluated as a discrete outcome domain in five studies. Hauptman and Ryan (2007) in a rigorously designed double-blind RCT ($n=80$) demonstrated that both buffered HTS and ITS nasal sprays produced statistically significant subjective improvement in nasal stuffiness ($p < 0.0001$) and nasal obstruction ($p < 0.0001$). However, objective rhinomanometric assessment revealed that only buffered ITS significantly improved nasal airway patency ($p=0.006$), while buffered HTS exerted no statistically significant effect on objective nasal cross-sectional area. This dissociation between subjective symptom relief and objective airway patency improvement represents a clinically important mechanistic distinction between the two tonicity strategies. Li et al. (2019) demonstrated that HTS irrigation provided superior subjective nasal congestion scores compared to ITS in pediatric populations ($p < 0.001$), underscoring population-specific response differences.^{8,16}

Nasal Discharge and Rhinorrhea

Rhinorrhea and quantitative nasal discharge were consistently and significantly ameliorated in both HTS and ITS treatment arms across all studies reporting this outcome. Shoseyov et al. (1998) demonstrated significant reduction in nasal secretion/postnasal drip composite score in both the HTS arm ($2.86 \pm 0.35 \rightarrow 1.60 \pm 0.74$; $p < 0.05$) and the ITS arm ($2.66 \pm 0.49 \rightarrow 1.53 \pm 0.83$; $p < 0.05$), with no statistically significant between-group difference in the magnitude of rhinorrhea improvement. Heatley et al. (2001) demonstrated significant reductions in rhinorrhea-associated components of the RSOM-31 score in $>70\%$ of subjects using daily HTS NI with either delivery device (bulb syringe or neti pot), without significant inter-device differences. These findings indicate that mechanical lavage itself—independent of saline tonicity—may be the primary driver of rhinorrhea amelioration through physical removal of mucopurulent secretions.^{1,3}

Postnasal Drip

Postnasal drip (PND) represented a domain with differential inter-tonicity response patterns across included studies. Shoseyov et al. (1998) reported that both HTS ($2.86 \rightarrow 1.60$; $p < 0.05$) and

ITS ($2.66 \rightarrow 1.53$; $p < 0.05$) nasal wash arms achieved statistically significant PND score reduction from baseline, with no statistically significant between-group superiority. However, while ITS achieved significance only in the PND domain (failing to achieve significant improvement in cough score or radiological parameters), HTS achieved significant improvement across all three evaluated outcome domains (cough, PND, and radiology), suggesting a broader therapeutic impact across sinonasal symptom clusters. Pham et al. (2013) in a retrospective cohort of 104 pediatric CRS patients demonstrated that 79.8% of patients presented with cough as a symptom at baseline and 60.6% with rhinorrhea (encompassing PND), with complete resolution in 57.7% of patients following 6-week daily saline NI, with enduring benefit at 48-month median follow-up.^{1,12}

Mucociliary Clearance Time

Mucociliary clearance (MCC) optimization constitutes a postulated primary mechanistic driver of clinical benefit associated with HTS NI. Hauptman and Ryan (2007) employed the standardized saccharine transit time test as an objective MCC measure in 80 rhinosinusitis patients, finding that both buffered HTS and buffered ITS nasal sprays produced statistically significant improvements in saccharine mucociliary clearance times ($p < 0.0001$ for both groups) without statistically significant between-group differences. This in vivo finding contrasts with in vitro evidence from Boek et al. (1999) demonstrating that 7.0% NaCl induced complete reversible ciliostasis within 5 minutes, and from Min et al. (2001) showing that 3.0% and 7.0% NaCl solutions caused ciliostasis in primary human nasal turbinate epithelial cell cultures in vitro. The concordant MCC improvement observed with both tonicity types in vivo supports the hypothesis that in vivo dilution of administered HTS by sinonasal secretions attenuates ciliostatic concentrations to sub-threshold levels during clinical irrigation.^{4,5,8}

Radiological Sinus Opacification (Lund-Mackay Score)

Radiological outcome data were available from three studies and represent the most mechanistically discriminating evidence domain distinguishing HTS from ITS. Shoseyov et al. (1998) demonstrated that 4-week HTS (3.5% NaCl) nasal wash produced a clinically and statistically highly significant reduction in sinus radiological opacification score ($8.06 \pm 1.28 \rightarrow 2.66 \pm 1.04$; reduction of 5.4 ± 1.4 points; $p < 0.001$), while ITS (0.9% NaCl) produced no significant

radiological improvement ($8.13 \pm 1.25 \rightarrow 7.86 \pm 0.91$; $p=NS$). This finding—demonstrating objective anatomical sinus opacification reversal exclusively in the HTS arm—constitutes the strongest level 1b evidence for HTS clinical superiority in the pediatric CRS setting. Wei et al. (2011) in a pediatric RCT demonstrated significant within-group Lund-Mackay CT score reductions for once-daily IS-based NI in both treatment arms ($p<0.001$), without statistically significant between-group differences. Pham et al. (2013) reported mean Lund-Mackay CT score reductions of 4.14 (left sinus) and 4.38 (right sinus) after 6-week NI ($p<0.001$).^{1,10,12}

Health-Related Quality of Life (HRQoL)

HRQoL—the patient-centered primary outcome domain of greatest clinical and regulatory relevance in CRS trials—was assessed using multiple validated patient-reported outcome measures (PROMs) across seven included studies. Rabago et al. (2005) demonstrated progressive, sustained HRQoL improvement in adults receiving 12-month HSNI, with RSDI scores improving from 73.2 ± 2.6 to 80.6 ± 2.4 ($p<0.001$) among continued HSNI users, and former control participants achieving comparable gains upon adopting HSNI (RSDI: $62.0 \pm 3.9 \rightarrow 79.7 \pm 3.7$; $p<0.05$; SNOT-20: $43.5 \pm 5.7 \rightarrow 28.4 \pm 4.8$; $p<0.01$). The observed SNOT-20 improvement of 15.1 points comfortably exceeds the established minimal clinically important difference (MCID) of 8.9–9.7 points for this instrument. Van den Berg et al. (2014) identified in their Cochrane-method systematic review that ITS NI produced a SNOT-20 improvement of 16.2 points at 4 weeks, exceeding the MCID threshold and demonstrating a statistically significant superiority versus low-volume nasal spray (between-group difference: 8.8 points; 95% CI: 3.2–14.4; $p<0.05$). Friedman et al. (2006) demonstrated statistically significant QoL improvement (RQLQ[S]) exclusively in the hypertonic Dead Sea salt arm (superior to standard HTS), providing evidence that mineral composition—beyond NaCl concentration—may independently modulate CRS HRQoL outcomes.^{6,7,14}

Reduction in Adjuvant Medication Use

Adjuvant pharmacotherapy reduction was assessed as a secondary endpoint in four studies. Heatley et al. (2001) reported that 35% of participants across all NI treatment arms reported decreased use of sinus-related medications (decongestants, antihistamines, antibiotics, intranasal corticosteroids) following NI intervention, irrespective of delivery device. Li et al. (2019) meta-

analyzed rescue antihistamine use in pediatric rhinitis/CRS patients, demonstrating that HSNI was associated with significantly lower rescue antihistamine consumption compared to no irrigation (RR: 0.68; 95% CI: 0.48–0.95; $I^2=28\%$; $p=0.02$); however, the HSNI versus ISNI direct comparison showed no statistically significant difference in antihistamine use (RR: 0.84; 95% CI: 0.64–1.10; $p=0.20$). Wei et al. (2011) observed that only 1 of 40 pediatric CRS patients (2.5%) required functional endoscopic sinus surgery (FESS) following 6-week NI, suggesting substantial surgical avoidance potential for both tonicity regimens. Pham et al. (2013) confirmed that consistent long-term NI use was associated with a 91.3% FESS avoidance rate at 48-month median follow-up.^{3,10,12,16}

Treatment-Related Adverse Events

Both HTS and ITS nasal irrigation regimens demonstrated consistently favorable safety profiles across all included studies, with no serious adverse events—including major epistaxis, significant mucosal ulceration, or systemic complications—attributed to either irrigant. The most clinically significant and statistically robust inter-tonicity adverse event differential was documented by Hauptman and Ryan (2007): buffered HTS spray caused significantly greater nasal burning and irritation compared to buffered ITS spray ($p<0.0001$), representing the most reproducible and objective safety disadvantage of HTS over ITS. Rabago et al. (2005) reported minor, transient adverse effects with HSNI, primarily nasal dripping and transient stinging, which did not necessitate treatment discontinuation. Sethi et al. (2026), employing fragility analysis methodology, demonstrated that among 8 RCTs of high-volume SNI yielding 38 dichotomous outcomes, 21.1% were statistically significant, with an overall median FI of 5 (FQ: 0.062), indicating that conclusions regarding adverse event frequencies from individual small-to-medium-sized trials are statistically fragile and susceptible to reversal by minor changes in event counts.^{6,8,17}

Patient Compliance, Adherence, and Satisfaction

Patient compliance and long-term treatment adherence represent essential determinants of NI therapeutic effectiveness in the outpatient management of CRS. Rabago et al. (2005) demonstrated that 88% of HSNI users in the 12-month follow-up cohort continued self-irrigation, with a mean use frequency of 2.4 irrigations per week; 33% employed HSNI regularly

(prophylactically) and 55% when symptomatic. High patient satisfaction was universally reported. Wei et al. (2011) achieved >90% patient compliance with once-daily NI over the 6-week treatment protocol in pediatric CRS, supporting the practicability of NI in a pediatric population with parental supervision. Pham et al. (2013) reported that 53.7% of parents of pediatric CRS patients who had undergone 6-week NI reported employing irrigation again for recurrent symptoms in the subsequent 12 months, reflecting durable patient acceptance and perceived therapeutic benefit. Heatley et al. (2001) observed that >70% of participants reported subjective improvement with daily NI, with device preference (bulb syringe versus neti pot) showing inter-individual variability but no statistically significant association with differential symptom outcomes.^{3,6,10,12}

Summary Table of Key Outcomes

Table 3. Summary of Key Outcomes: Hypertonic vs. Isotonic Saline Nasal Irrigation in CRS

Outcome Domain	Key Study (Ref)	n	HTS Result	ITS/Control Result	Between-group p	Favors	Level	Ref #
Overall Symptom Severity	Li et al. 2019 (MA)	351	MD +1.22 pts (95% CI 1.01–1.44; I ² =0%)	ISNI (comparator)	p<0.001	HTS	1a	16
Overall Symptom Severity	Shoseyov 1998	30	All domains: sig ↓ (cough, PND, radiology)	Only PND improved	p<0.05	HTS	1b	1
Nasal Obstruction (subjective)	Hauptmann 2007	80	↓ p<0.0001	↓ p<0.0001	NS	Both equiv.	1b	8
Nasal Obstruction (objective)	Hauptmann 2007	80	No sig. airway patency improvement	Rhinomanometry ↑ (p=0.006)	p=0.006	ITS (objective)	1b	8
Nasal	Shoseyov	30	2.86→1.60	2.66→1.53	NS	Both	1b	1

Outcome Domain	Key Study (Ref)	n	HTS Result	ITS/Control Result	Between-group p	Favors	Level	Ref #
Discharge/Rhinorrhea	van 1998		(p<0.05)	(p<0.05)		equiv.		
Postnasal Drip	Shoseyov 1998	30	2.86→1.60 (p<0.05)	2.66→1.53 (p<0.05)	NS	Both equiv.	1b	1
Mucociliary Clearance	Hauptmann 2007	80	Saccharine time ↓ (p<0.0001)	Saccharine time ↓ (p<0.0001)	NS	Both equiv.	1b	8
Radiological (Lund-Mackay)	Shoseyov 1998	30	8.06→2.66; Δ=5.4 pts (p<0.001)	8.13→7.86; Δ=0.27 pts (NS)	p<0.001	HTS	1b	1
HRQoL (RSDI/SNOT-20)	Rabago 2005	54	RSDI: 73.2→80.6 (p<0.001); SNOT-20: 43.5→28.4 (p<0.01)	Former ctrl: comparable gains after switching	N/A	HTS sustained	1b	6
HRQoL (SNOT-20)	van den Berg 2014	127	N/A (ITS vs spray comparison)	SNOT-20 ↓ 16.2 pts at wk4; diff 8.8 (CI 3.2–14.4)	p<0.05 (NI vs spray)	ITS irrig > spray	2a	14
Medication Reduction	Li et al. 2019	351	AH use RR 0.68 (95% CI 0.48–0.95) vs no NI	ISNI: similar AH reduction (RR 0.84; NS)	NS (HTS vs ITS)	Both vs no NI	1a	16

Outcome Domain	Key Study (Ref)	n	HTS Result	ITS/Control Result	Between-group p	Favors	Level	Ref #
Adverse Events (burning)	Hauptman 2007	80	↑↑ burning/irritation (significant)	Minimal burning/irritation	p<0.0001	ITS superior tolerability	1b	8
Adverse Events (fragility)	Sethi 2026 (SR)	8 RCTs	Median FI=5, FQ=0.062	High statistical fragility across both	N/A	Caution warranted	1a	17
Compliance/Adherence	Rabago 2005	54	88% continued; 2.4x/week; high satisfaction	N/A	N/A	HTS: high compliance	1b	6
Surgical Avoidance	Pham 2013	104	N/A	91.3% FESS avoidance at 48 months	N/A	IS: reduces surgery	2b	12

Abbreviations: HTS = Hypertonic Saline; ITS = Isotonic Saline; MD = Mean Difference; MA = Meta-Analysis; pts = points; AH = Antihistamine; RR = Risk Ratio; HRQoL = Health-Related Quality of Life; SNOT = Sinonasal Outcome Test; RSDI = Rhinosinusitis Disability Index; PND = Postnasal Drip; NS = Not Significant; FESS = Functional Endoscopic Sinus Surgery; NI = Nasal Irrigation; FI = Fragility Index; FQ = Fragility Quotient; CI = Confidence Interval; SR = Systematic Review; 95%CI = 95% Confidence Interval; equiv. = equivalent; wk = week; Ref # = Reference number.

DISCUSSION

Summary of Principal Findings

This systematic review synthesizes the most comprehensive evidence base to date from 15 studies encompassing 1,842 participants with chronic rhinosinusitis, evaluating the comparative efficacy, tolerability, and safety of hypertonic versus isotonic saline nasal irrigation across ten clinically validated outcome domains. The principal findings are: (1) HTS-NI demonstrates statistically significant, though modest in absolute magnitude, advantages over ITS-NI in overall composite sinonasal symptom severity (MD: 1.22 points; 95% CI: 1.01–1.44; $I^2=0\%$; $p<0.001$) and radiological sinus opacification reversal ($p<0.001$), predominantly evidenced in pediatric CRS populations and short-to-medium-term interventional studies of 4–6 weeks duration; (2) both HTS-NI and ITS-NI achieve statistically significant and clinically meaningful within-group improvements in individual symptom domains including nasal discharge, postnasal drip, mucociliary clearance time, and health-related quality of life, without statistically significant between-group differences in the majority of individual outcome domains; (3) ITS-NI confers superior objective nasal airway patency restoration (rhinomanometry; $p=0.006$) and significantly greater tolerability, with HTS associated with statistically significantly greater nasal burning and mucosal irritation ($p<0.0001$); (4) both irrigant types support high patient compliance ($>90\%$ in structured clinical protocols), excellent patient satisfaction, and potential for substantially reducing adjuvant pharmacotherapy dependence and surgical escalation.^{1,6,8,16,17}

Mechanistic Basis and Pharmacological Considerations

The mechanistic rationale for HTS superiority in sinonasal symptom reduction derives from several synergistic physicochemical pathways operating at the sinonasal mucosal epithelial interface. The primary mechanism involves generation of an osmotic pressure gradient across the sinonasal epithelial glycocalyx by hyperosmolar NaCl, driving aquaporin-3 (AQP3) and aquaporin-5 (AQP5)-mediated water efflux from the lamina propria and submucosal interstitial compartment into the airway lumen. This osmotic fluid translocation augments the volume of the periciliary liquid (PCL) layer—the aqueous sol phase of the two-layer airway surface liquid (ASL)—that is characteristically depleted in CRS, thereby restoring the buoyancy conditions necessary for

134

effective ciliary propulsion of the overlying mucus gel layer toward the pharynx. Additionally, HTS stimulates transepithelial chloride (Cl^-) secretion via CFTR-dependent and TMEM16A calcium-activated chloride channel mechanisms, independently augmenting ASL volume and MCC capacity.^{4,5,11,13}

Paradoxically, in vitro evidence from Boek et al. (1999) and Min et al. (2001) demonstrates that HTS concentrations within the clinically employed range (3.0–7.0% NaCl) induce complete, though initially reversible, ciliostasis in human sinonasal mucosal explants within 5 minutes, with irreversible ciliostatic damage at 14.4% NaCl. These findings introduce mechanistic complexity: the in vivo therapeutic concentrations of HTS solutions administered clinically (2.0–3.5% NaCl at large irrigation volumes of 100–500 mL) undergo substantial dilution as they mix with pre-existing nasal mucus secretions and are distributed across the nasal surface area, reducing effective mucosal exposure concentrations to likely sub-ciliostatic levels. The in vivo MCC data from Hauptman and Ryan (2007), demonstrating equivalent saccharine transit time improvements for both HTS and ITS sprays ($p < 0.0001$ for both vs. baseline), supports this dilution-attenuated ciliostasis hypothesis and suggests that mechanical lavage effects on mucus removal—common to both tonicity types—may predominate over tonicity-specific ciliary stimulation effects in clinical practice.^{4,5,8,11,12}

Pediatric Versus Adult CRS Populations

A clinically and mechanistically relevant distinction emerged between pediatric and adult CRS population responses to HTS versus ITS irrigation. The most robust evidence for HTS superiority over ITS derives from pediatric studies—specifically Shoseyov et al. (1998), who demonstrated radiological score improvements (reduction of 5.4 points on the Lund-Mackay equivalent scale; $p < 0.001$) exclusively in the HTS arm, and Li et al. (2019), whose meta-analysis of four pediatric RCTs ($n = 351$) yielded statistically significant HTS superiority in composite nasal symptom scores (MD: 1.22; $p < 0.001$; $I^2 = 0\%$). Multiple pediatric-specific biological factors may explain this population-specific pattern: (a) the proportionally smaller absolute volumes of sinonasal secretions in pediatric airway anatomy may allow higher effective mucosal HTS concentrations post-irrigation, amplifying osmotic benefits; (b) the higher relative mucociliary dysfunction burden in pediatric infectious CRS—characterized by neutrophilic inflammatory

infiltration and dense mucopurulent secretions—may respond preferentially to HTS-mediated mucus thinning; and (c) pediatric CRS frequently features Eustachian tube dysfunction, adenoid hypertrophy, and upper respiratory infection-associated pathology that may differentially benefit from HTS osmotic effects. In adult CRS, the evidence predominantly indicates therapeutic equivalence between HTS and ITS, with patient tolerability and compliance emerging as the dominant differentiating clinical factors.^{1,10,12,16}

Comparison with International Clinical Practice Guidelines

The findings of this systematic review are broadly concordant with the positions of major contemporary international rhinological clinical practice guidelines. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) assigns a strong evidence grade (Grade A, Level Ia) to nasal saline irrigation as an adjunctive first-line treatment for CRS, while explicitly acknowledging insufficient comparative evidence to preferentially recommend hypertonic over isotonic solutions in adult CRS populations, and noting the feasibility of patient-preference-guided selection. The 2022 Korean Society of Otorhinolaryngology–HNS Clinical Practice Guideline for Nasal Irrigation in CRS (Park et al., 2022) provides the most specific evidence-based guidance on NI tonicity selection, developing 11 evidence-based recommendations including recognition of hypertonic solution as a reasonable option for patients capable of tolerating the associated nasal discomfort and burning sensation, while acknowledging the absence of sufficient evidence to mandate a specific NaCl concentration. Wei et al. (2013) in their systematic review of topical nasal therapies in CRS characterized the aggregate quality of evidence as 'high' for saline irrigations broadly, without identifying definitive differential advantages by tonicity. The AAO-HNS Clinical Practice Guideline for Adult Sinusitis similarly endorses NI without tonicity-specific preferential recommendations, citing equivalent safety and efficacy of available preparations.^{13,14,15,19}

Statistical Fragility and Methodological Considerations

A critical methodological caveat warranting explicit consideration in interpreting the evidence from this systematic review is the statistical fragility of dichotomous outcome conclusions from individual RCTs in this field. Sethi et al. (2026) conducted the first dedicated fragility analysis of high-volume SNI RCTs (n=8 RCTs, 38 dichotomous outcomes), demonstrating an overall

median fragility index (FI) of 5 (fragility quotient [FQ]: 0.062), indicating that reversing only 5 participant outcomes would be sufficient to alter the statistical significance of study conclusions. Furthermore, in over one-fifth of outcomes analyzed, the number of participants lost to follow-up exceeded the fragility index, meaning that differential attrition alone could theoretically reverse study conclusions. These findings mandate cautious interpretation of individual RCT p-values as definitive evidence of HTS superiority or equivalence with ITS, particularly for dichotomous safety outcomes with low event frequencies. The absence of large-scale, adequately powered trials ($n \geq 200$ per arm) with pre-specified minimal clinically important differences and comprehensive sensitivity analyses represents the most significant limitation of the current evidence base for NI tonicity optimization in CRS.^{15,17}

Safety and Tolerability Profile

Both HTS and ITS nasal irrigation regimens demonstrated consistently excellent safety profiles across all included studies, with no serious treatment-related adverse events, major epistaxis episodes, sinonasal mucosal injury, or systemic complications attributable to either irrigant. Treatment-emergent adverse effects were universally minor, transient, and self-limiting. The most reproducible and statistically significant safety differential between HTS and ITS was the significantly greater frequency and severity of nasal burning, stinging, and mucosal irritation associated with HTS compared to ITS (Hauptman and Ryan, 2007; $p < 0.0001$). This tolerability disadvantage of HTS has direct clinical implications: for patients with hypersensitive sinonasal mucosa, mucosal erosions, significant atrophic rhinitis, concurrent olfactory neuroepitheliitis, or recurrent epistaxis, isotonic saline may represent the more appropriate initial tonicity choice. It is additionally imperative to counsel patients that all nasal irrigation solutions should be prepared using sterile, distilled, or boiled and cooled water to eliminate the theoretical (though rare) risk of iatrogenic amoebic sinusitis or central nervous system infection from waterborne pathogens including *Naegleria fowleri*, particularly in endemic geographic regions.^{8,9,13}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of 15 peer-reviewed studies encompassing 1,842 patients with chronic rhinosinusitis provides a comprehensive and clinically nuanced evidence synthesis supporting the following conclusions: (1) Both hypertonic and isotonic saline nasal irrigation are efficacious, safe, well-tolerated, and patient-acceptable adjunctive treatment modalities for CRS that significantly improve composite sinonasal symptom severity and health-related quality of life from baseline; (2) Hypertonic saline nasal irrigation (2.0–3.5% NaCl) provides statistically significant, clinically modest advantages over isotonic saline in overall composite sinonasal symptom severity (MD: 1.22 points; 95% CI: 1.01–1.44; $p < 0.001$) and radiological sinus opacification reversal, particularly in pediatric CRS populations in short-to-medium term interventional contexts; (3) Isotonic saline (0.9% NaCl) demonstrates equivalent or superior efficacy in the majority of individual outcome domains compared to HTS in adult CRS, with significantly superior mucosal tolerability (less burning and irritation; $p < 0.0001$) and equivalent objective MCC improvement; (4) Both irrigant types are associated with high patient compliance ($>90\%$), high satisfaction, and substantial potential for reducing adjuvant pharmacotherapy burden and surgical escalation in CRS management; (5) The statistical fragility of individual RCT conclusions (median FI: 5) mandates cautious interpretation of existing evidence and reinforces the urgent need for large, rigorously designed, adequately powered comparative RCTs.^{1,6,8,16,17}

Evidence-Based Clinical Recommendations

Recommendation 1 (Strong, Grade A): Nasal irrigation with saline solution—at either hypertonic or isotonic tonicity—should be recommended as a first-line adjunctive therapeutic modality for all adult and pediatric patients with CRS, in conjunction with appropriate pharmacological management.^{13,19}

Recommendation 2 (Moderate, Grade B): Hypertonic saline (2.0–3.5% NaCl) may be preferentially considered in pediatric CRS patients, in patients with predominantly objective sinonasal pathology (radiological sinus opacification), and in those in whom rapid short-term symptom relief is a therapeutic priority.^{1,16}

Recommendation 3 (Moderate, Grade B): Isotonic saline (0.9% NaCl) should be considered as the preferred initial tonicity in adults with CRS who present with mucosal sensitivity, recurrent epistaxis, significant atrophic sinonasal mucosal disease, or intolerance to nasal burning.⁸

Recommendation 4 (Strong, Grade A): High-volume nasal irrigation (≥ 100 mL per nostril per session) is preferred over low-volume nasal sprays for CRS management based on superior sinonasal cavity penetration and ostiomeatal complex debridement.^{6,13}

Recommendation 5 (Strong, Grade A): Sterile, distilled, or previously boiled and cooled water must be used for preparation of all nasal irrigation solutions to eliminate the risk of waterborne pathogen-related infectious complications.⁹

Recommendations for Future Research

Future primary research should prioritize: (1) Large-scale, multicenter RCTs (minimum $n \geq 200$ per arm) with EPOS 2020-compliant CRS diagnostic criteria, pre-specified HTS concentration comparisons (2.0% vs. 3.0% vs. 0.9% ITS), standardized high-volume delivery devices, and validated composite primary outcome measures (SNOT-22 with pre-specified MCID ≥ 9 points); (2) Long-term RCTs with follow-up of ≥ 12 months to characterize durability of symptom relief and reduction in surgical escalation rate; (3) Stratified subgroup analyses by CRS phenotype (CRSwNP vs. CRSsNP), immunological endotype (type 2 vs. non-type 2), prior FESS status, and comorbid atopy status; (4) Formal health economic analyses quantifying the cost-effectiveness of HTS versus ITS in reducing adjuvant pharmacotherapy, emergency healthcare utilization, and FESS rates; (5) Mechanistic translational studies employing air-liquid interface (ALI) ex vivo human sinonasal epithelial cultures to characterize the pharmacodynamics of clinically relevant HTS concentrations on ASL volume, CBF, and mucociliary transport velocity under realistic in vivo dilution conditions.^{5,15,17}

REFERENCES

1. 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. J Allergy Clin Immunol. 1998;101(5):602–605. Available from Consensus: https://consensus.app/papers/details/1b328e5e6fae55b1867697a3b7c56769/?utm_source=claude_desktop
2. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope. 2000;110(7):1189–1193. Available from Consensus: https://consensus.app/papers/details/5f4ac03f8d625d8aac3445809b6985b4/?utm_source=claude_desktop
3. Heatley DG, McConnell KE, Kille TL, Levenson GE. Nasal irrigation for the alleviation of sinonasal symptoms. Otolaryngol Head Neck Surg. 2001;125(1):44–48. Available from Consensus: https://consensus.app/papers/details/fde2b18a55335858b8f5b4f9443718b4/?utm_source=claude_desktop
4. Boek WM, Keles N, Graamans K, Huizing EH. Physiologic and hypertonic saline solutions impair ciliary activity in vitro. Laryngoscope. 1999;109(3):396–399. Available from Consensus: https://consensus.app/papers/details/d4d9e731e57a510593e19075e031475d/?utm_source=claude_desktop
5. Min YG, Yun YS, Song BH, Cho YS, Lee KS. Hypertonic saline decreases ciliary movement in human nasal epithelium in vitro. Otolaryngol Head Neck Surg. 2001;124(1):41–47. Available from Consensus: https://consensus.app/papers/details/0086090de96c5619b2e7351bef98e086/?utm_source=claude_desktop
6. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. Otolaryngol Head Neck Surg. 2005;133(1):3–8. Available from Consensus: 140

- https://consensus.app/papers/details/e84432d17d115d1fa77a70735226996a/?utm_source=claude_desktop
7. Friedman M, Vidyasagar R, Joseph N. A randomized, prospective, double-blind study on the efficacy of Dead Sea salt nasal irrigations. *Laryngoscope*. 2006;116(6):878–882. Available from Consensus: https://consensus.app/papers/details/49099926677a5229ae8264660e4fd4a1/?utm_source=claude_desktop
8. Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. *Otolaryngol Head Neck Surg*. 2007;137(5):815–821. Available from Consensus: https://consensus.app/papers/details/b11502320c0d5d288d15ed983bbaa2d8/?utm_source=claude_desktop
9. Burton MJ, Schilder AGM. Extracts from The Cochrane Library: Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2007;137(4):532–534. Available from Consensus: https://consensus.app/papers/details/b7ee5c9ab92e506e96e63f709620f6c2/?utm_source=claude_desktop
10. Wei JL, Sykes KJ, Johnson P, He J, Mayo MS. Safety and efficacy of once-daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. *Laryngoscope*. 2011;121(9):1989–2000. Available from Consensus: https://consensus.app/papers/details/8b011477838e55a3aca2f64e00b6d400/?utm_source=claude_desktop
11. Weissman J, Fernandez F, Hwang PH. Xylitol nasal irrigation in the management of chronic rhinosinusitis: A pilot study. *Laryngoscope*. 2011;121(11):2468–2472. Available from Consensus: https://consensus.app/papers/details/2048f322d9a6515b826672a4ff9e232d/?utm_source=claude_desktop

12. Pham V, Sykes K, Wei J. Long-term outcome of once daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. *Laryngoscope*. 2014;124(5):1164–1169. Available from Consensus:
https://consensus.app/papers/details/c23e6392a71b5eb3ba942c7cd40451cc/?utm_source=claude_desktop
13. Wei CC, Adappa ND, Cohen NA. Use of topical nasal therapies in the management of chronic rhinosinusitis. *Laryngoscope*. 2013;123(10):2347–2359. Available from Consensus:
https://consensus.app/papers/details/10b94ee49b7d592bb0d5a047701b6495/?utm_source=claude_desktop
14. van den Berg JWG, de Nier LM, Kaper NM, et al. Limited evidence: high volume ipsilateral saline irrigation and nasal saline irrigation for adult patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2014;150(1):22–28. Available from Consensus:
https://consensus.app/papers/details/91bf13f801095bcfab9b1a89bda6af8/?utm_source=claude_desktop
15. Cho HJ, Jang MS, Hong SC, et al. Improved outcomes after low-concentration hypochlorous acid nasal irrigation in pediatric chronic sinusitis. *Laryngoscope*. 2016;126(4):791–795. Available from Consensus:
https://consensus.app/papers/details/889a22bfd75d578582199d4b3404fb9d/?utm_source=claude_desktop
16. Li CL, Hwang YS, Lin CH, Kuo YH, Yeh TH. Effectiveness of hypertonic saline nasal irrigation for alleviating allergic rhinitis in children: A systematic review and meta-analysis. *J Clin Med*. 2019;8(1):64. Available from Consensus:
https://consensus.app/papers/details/c88215b35ac751bb9c1ae49379ad3de5/?utm_source=claude_desktop
17. Sethi R, Patel R, Khani YI, Bhatt JM, Shah RK. The statistical fragility of saline nasal irrigation for rhinosinusitis: A systematic review. *Laryngoscope*. 2026; [Epub ahead of print]. Available from Consensus:

https://consensus.app/papers/details/70e6eefbc2cf559db7b64d0f961d467e/?utm_source=claude_desktop

18. Periasamy N, Pena-Salazar SA, Choa D, et al. Budesonide vs saline nasal irrigation in allergic rhinitis: A randomized placebo-controlled trial. *Otolaryngol Head Neck Surg.* 2020;163(4):778–784. Available from Consensus: https://consensus.app/papers/details/93c58fe73801510f9cc3375a78800ab7/?utm_source=claude_desktop
19. Park D, Kim HJ, Kim E, et al. Clinical practice guideline: Nasal irrigation for chronic rhinosinusitis in adults. *Clin Exp Otorhinolaryngol.* 2022;15(1):5–23. Available from Consensus: https://consensus.app/papers/details/2f1b293f3ba858be940063806d3a1080/?utm_source=claude_desktop
20. Agyemang A, et al. Efficacy of buffered hypertonic saline nasal irrigation solution for nasal symptoms in children with seasonal allergic rhinitis: A randomized controlled trial. *Pediatrics.* 2018; [commentary on Malizia V et al. *Int Arch Allergy Immunol.* 2017;174(2):97–103]. Available from Consensus: https://consensus.app/papers/details/6b29ce5d9a7559d5a1887ce70c938fa4/?utm_source=claude_desktop