

Topical Irrigations for Chronic Rhinosinusitis



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KEYWORDS

- Topical therapies • Irrigations • Chronic rhinosinusitis • Saline • Topical steroids
- Topical antibiotics • Topical antifungals • Manuka honey

KEY POINTS

- Saline irrigations and topical corticosteroid sprays are recommended in the treatment of chronic rhinosinusitis.
- Topical corticosteroid irrigations are recommended as an option particularly in the post-operative setting. Further research on their effect on the hypothalamic-pituitary-adrenal axis is needed.
- Topical antibiotics are not recommended in the treatment of routine chronic rhinosinusitis but may have a role in recalcitrant cases.
- Topical antifungals are not recommended, but their effect in the allergic fungal subtype is unclear and warrants further investigation.
- Investigations are underway on a variety of topical alternative therapies, with additional ones, such as topical probiotics, on the horizon.

INTRODUCTION

The sinonasal cavity is easily accessible and therefore particularly amenable to topical therapy. Topical therapy offers multiple advantages over systemic therapy. It is administered directly onto the affected tissue, has the potential to be delivered at higher local concentrations, and minimizes systemic absorption, thereby reducing the potential for adverse systemic effects.¹ The existing data support optimal sinus delivery using a high-volume irrigation device, and in surgically opened sinuses and the head down and forward position.^{2–6}

Saline irrigations are the oldest and most widely used of the topical therapies. As the understanding of the primary cause of chronic rhinosinusitis (CRS) has shifted away from infection toward inflammation, topical corticosteroid sprays have also become a mainstay of treatment with irrigations an option in the postoperative setting. The

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popularity of topical antibiotics has subsequently waned with their use reserved for recalcitrant cases, and the use of topical antifungals is now defunct in the treatment of routine CRS. In recent years with the growing concern over the role of biofilms in CRS, topical alternative therapies that target biofilms, such as surfactants and manuka honey, have also gained increasing recognition. This article summarizes the existing literature on the various topical therapies that have been studied, also highlighting exciting new avenues of research, such as topical probiotics.⁵

SALINE IRRIGATIONS

Indications

The proposed physiologic benefits of nasal saline irrigations include improved mucociliary clearance and disruption and removal of mucus, blood, and environmental allergens.^{7,8} Nasal saline irrigations are indicated as an adjunct to other medical therapies for CRS. A 2007 systematic review with metanalysis by Harvey and colleagues⁹ included eight randomized controlled trials (RCTs) with a variety of study designs, comparing saline with no treatment, placebo, or as an adjunct to other treatments. The study concluded that the benefits of saline outweigh the drawbacks and that saline may be used as an adjunctive treatment of CRS, because it seemed to improve symptoms as a sole treatment modality but was less effective compared with intranasal corticosteroid (INCS) therapy.⁹ The 2013 evidence-based reviews by Rudmik and colleagues¹ and Wei and colleagues¹⁰ reached similar conclusions, as did the 2016 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis.⁵

Saline irrigations may also be useful in the immediate postoperative period for patients that have undergone endoscopic sinus surgery (ESS). An RCT by Liang and colleagues¹¹ found that saline irrigations combined with postoperative debridement improved symptoms and endoscopic appearance compared with debridement alone in the mild CRS group, although not in the moderate-severe CRS group. In another RCT, Freeman and colleagues¹² noted improved endoscopic appearance and mucociliary function at 3 weeks with saline irrigations, but these improvements were not sustained at 3 months. The study, however, used a suboptimal low-volume delivery protocol, and it is difficult to determine the extent to which this may have contributed to the lack of sustained improvement. The 2016 International Consensus Statement on Allergy and Rhinology: Rhinosinusitis has recommended nasal saline irrigations for postoperative care.⁵

Volume, Formulations, and Cost

Studies support the superiority of high-volume irrigations over low-volume sprays and nebulizers. In an RCT by Pynnonen and colleagues,¹³ patients with chronic sinus and nasal symptoms that received high-volume irrigations achieved lower Sino-Nasal Outcome Test (SNOT)-20 scores compared with patients that received nasal spray over an 8-week period. The use of high-volume nasal saline irrigations, defined as greater than 200 mL, is recommended over low-volume methods.⁵ The cost of high-volume irrigation devices is also favorably low, estimated at approximately \$0.24 per day.⁵

In addition to determining optimal volume, studies have focused on evaluating which saline formulation, isotonic versus hypertonic, is most effective. Studies comparing isotonic and hypertonic saline irrigations have shown that both improved symptoms but there were no significant differences between the groups.^{14,15} Overall, the data do not support a difference in effectiveness between isotonic and hypertonic formulations.^{1,9}

Safety Profile

Saline irrigations are generally well-tolerated.⁵ The most frequently reported adverse effects are nasal burning, local irritation, and nausea. Headaches, epistaxis, postnasal drainage, and ear pain/congestion have also been reported.^{5,8} These side effects may occur more frequently with hypertonic solutions.⁵

Although extremely rare, there have been deaths from amebic meningoencephalitis believed to be related to sinus irrigations with contaminated water. As a result, it is recommended to use a clean water source for irrigations, avoiding well/tap water, until this is better elucidated.¹⁶ Bacterial colonization of irrigation bottles is also well-known, but it does not seem to be associated with increased clinical infections in CRS.⁷ Nevertheless, it is suggested that patients regularly clean their nasal irrigation devices. Microwave decontamination has been suggested as a possible cleaning strategy.¹⁷

TOPICAL CORTICOSTEROIDS

Mechanism

Corticosteroids suppress inflammation via a variety of mechanisms. They reduce circulating leukocytes and inhibit proinflammatory transcription factors, arachidonic acid metabolites, histamine and leukotriene release from basophils, neuropeptide-induced inflammation, and lysozyme release. Corticosteroids also decrease vascular permeability, and inhibit glycoprotein release from submucosal glands, thinning mucus secretions.¹⁸

Indications

Standard delivery (sprays)

Standard INCS refers to metered-dose topical corticosteroid solutions that are approved by the Food and Drug Administration for nasal use. In patients with CRS without nasal polyposis (CRSsNP), systematic reviews with meta-analyses by Kalish and colleagues¹⁹ and Snidvongs and colleagues²⁰ have been performed evaluating standard INCS. Kalish and colleagues¹⁹ combined results from five RCTs and concluded there was no significant benefit with INCS, although there was significant heterogeneity between studies. Total symptom scores were reported in three of the trials; however, with a standardized mean difference favoring INCS, suggesting a symptom benefit.¹⁹ Snidvongs and colleagues²⁰ pooled symptom scores for five RCTs and found a significant improvement with INCS, with no significant heterogeneity between studies noted.

In patients with CRS with nasal polyposis (CRSwNP), systematic reviews with meta-analyses by Joe and colleagues,²¹ Rudmik and colleagues,²² and Snidvongs and colleagues²⁰ have been performed evaluating standard INCS. Pooled data demonstrated significant reduction in polyp size and significant symptom and nasal peak inspiratory flow improvement. A 2016 systematic review by Chong and colleagues²³ included 18 RCTs, 14 studies including patients with CRSwNP and 4 studies including patients with CRSsNP. The study concluded that there seemed to be an improvement for all symptoms.²³ Overall, standard delivery of topical corticosteroids is well-supported in the literature, and its use is recommended in CRSsNP and CRSwNP.⁵

Nonstandard delivery (irrigations)

Standard INCS, however, has limited distribution beyond the nasal cavities, especially in patients that have not undergone ESS.³ Nonstandard INCS refers to off-label therapies, such as high-volume topical corticosteroid irrigations, which are designed to

deliver a higher volume and concentration of corticosteroid.⁵ Despite the widespread use of these irrigations in clinical practice, there is a paucity of high-quality data.

Rotenberg and colleagues²⁴ in 2011 published an RCT evaluating the effect of budesonide irrigations in patients with Samter triad who had undergone ESS. Patients were randomized into three arms: (1) saline irrigation alone, (2) saline irrigation plus separate budesonide nasal spray, and (3) saline irrigation mixed with budesonide nasal spray. Outcome measures were symptom, radiographic, and endoscopic scores. All groups showed improvement in outcomes, but there were no significant differences among the groups.²⁴

Tait and colleagues²⁵ in 2018 published the only other RCT evaluating the effectiveness of high-volume budesonide irrigations in patients with CRS. Patients with and without polyps were enrolled. Sixty-one patients were included in the per-protocol analysis, 29 randomized to perform budesonide irrigations and 32 randomized to perform saline irrigations for 1 month. The budesonide group showed greater mean improvement in SNOT-22 and endoscopic scores compared with the saline group, although there were no significant differences between the groups. It is worth noting, however, that the budesonide group exceeded the minimal clinically important difference for the SNOT-22, whereas the saline group did not, suggesting that budesonide may have clinically meaningful benefits beyond saline alone.²⁵

Several less scientifically rigorous studies have also demonstrated significant improvements in outcomes with topical corticosteroid irrigations.²⁶ Given the conflicting results and overall lack of high-quality data, evidence-based reviews and consensus statements have found it challenging to provide a recommendation for or against the use of topical corticosteroid irrigations. They are currently recommended as an option in the treatment of CRSsNP and CRSwNP, especially in the post-operative setting.^{1,5}

Formulations and Cost

Standard sprays come in a variety of formulations.¹ Second-generation sprays have less than 2% systemic bioavailability compared with 10% to 50% for first-generation sprays.²⁷ There is insufficient evidence to recommend one spray formulation over another.²⁸ The most widely studied formulation of nonstandard high-volume topical corticosteroid irrigations is budesonide. Common formulations are listed in **Table 1**. The spray formulations are low in cost. The cost of the irrigations, however,

Table 1 Common formulations for topical corticosteroids		
	Class	Generic Name (Brand Name)
Standard (sprays)	1st generation	Beclomethasone (Beconase AQ, Qnasl)
		Budesonide (Rhinocort Aqua ^b)
		Triamcinolone (Nasacort AQ ^{a,b})
	2nd generation	Ciclesonide (Omnaris, Zetonna)
		Fluticasone (Veramyst ^a , Flonase ^b)
Nonstandard (irrigations)		Mometasone (Nasonex ^a)
		Budesonide (0.25–2 mg/2 mL in 240 mL saline)
		Mometasone

^a Indicates approved for age 2 and older.
^b Indicates available over-the-counter.
Adapted from Lee VS, Lin SY. Allergy and the Pediatric Otolaryngologist. *Otolaryngol Clin North Am* 2019;52(5):870; with permission.

is prohibitive for some patients because they are frequently not covered by insurance given their off-label usage. The increasing availability of special compounding pharmacies has helped to lower out-of-pocket costs.

Safety Profile

Given that the dosing of budesonide used in concentrated irrigations is much higher than in spray formulations, there is concern for unwanted systemic absorption that could lead to hypothalamic-pituitary-adrenal (HPA) axis suppression and/or increased intraocular pressure. Small studies looking at short-term use of budesonide irrigations, at least 6 to 8 weeks in duration, found no evidence of HPA axis suppression or increased intraocular pressure.^{29,30}

More recently, two studies have evaluated more long-term use of budesonide irrigations. Smith and colleagues³¹ completed a cross-sectional cohort study of 35 post-ESS patients with CRS who performed budesonide irrigations for at least 12 months. They concluded that there was no detectable HPA axis suppression. Soudry and colleagues³² evaluated 48 post-ESS patients with CRS who were treated with budesonide irrigations for at least 6 months. Of note, 32 of the 48 patients were also using other topical steroid formulations. Intraocular pressure was normal in all patients. Eleven of the 48 patients, however, had abnormally low stimulated cortisol levels on corticotropin stimulation testing, although they were not symptomatic. Four repeated the testing after stopping the budesonide irrigation for 30 days, and three had increased stimulated cortisol levels.³²

The current literature suggests that high-volume budesonide irrigations do not affect intraocular pressure but that there may be a low risk of HPA axis suppression with long-term use. Further research is needed to evaluate the true impact of long-term topical steroid irrigations on the HPA axis, especially in the setting of concomitant use of other topical steroid formulations. Determining this along with their clinical effectiveness will help to shape recommendations regarding their use in the future.

TOPICAL ANTI-INFECTIVES

Topical Antibiotics

CRS was once thought to be primarily the result of bacterial infection, fueling interest in topical antibiotic therapies. Over time, however, there has been a paradigm shift away from an infectious cause of CRS and toward an inflammatory one.⁸ Several RCTs and systematic reviews have examined topical antibiotics in CRS, primarily in the post-ESS setting, failing to show any benefit and recommending against their use because of lack of evidence.^{1,7,10,33–39}

Mupirocin irrigations have perhaps the strongest data supporting their use of any topical antibiotic. Jervis-Bardy and colleagues^{40,41} published an RCT studying the use of mupirocin irrigations to target *Staphylococcus aureus*. Twenty-two patients were included in the per-protocol analysis, 13 randomized to perform mupirocin irrigations and 9 randomized to perform saline irrigations for 1 month. The study demonstrated significant improvement in positive culture rates, although a high long-term microbiologic failure rate was reported in a follow-up study. Additionally, there were no significant improvements in symptom or endoscopic outcomes.^{40,41}

In summary, topical antibiotics are not recommended in the treatment of routine CRS. Some case series have reported benefit in recalcitrant cases, indicating that there may be a role for topical antibiotics in challenging cases ideally in a culture-directed fashion.⁵

Topical Antifungals

Since the 1990s, fungal elements have been known to be present in the sinonasal cavity in patients with CRS, and it was hypothesized that they were contributing to the inflammation in CRS. In 2002, a pilot study examining topical amphotericin B in patients with CRS showed promising improvements in symptom and endoscopic measures, driving a subsequent flurry of RCTs and metaanalyses that have overall failed to show any benefit.^{1,42–47}

Allergic fungal rhinosinusitis (AFRS) represents a unique subtype of patients with CRS, and fungi may play a greater role in its pathophysiology. Unfortunately, there are minimal data evaluating topical antifungal therapy in patients with AFRS specifically. Pilot data suggest that there may be some benefit, although the studies suffered from serious methodologic issues.^{44,48} In summary, topical antifungal therapy is not recommended in the treatment of CRSsNP or CRSwNP. Further research is needed to determine if it has any beneficial effects in AFRS specifically.

Formulations and Cost

Formulations of topical antibiotic therapy are directed toward the presumed pathogen. The most frequently implicated pathogenic bacteria in CRS are *S aureus*, targeted most commonly with mupirocin irrigations, and *Pseudomonas aeruginosa*, targeted most commonly with tobramycin irrigations. The most widely studied formulation of topical antifungal therapy is amphotericin B. Like topical corticosteroid irrigations, the cost for topical anti-infective irrigations is high and is often not covered by insurance. Special compounding pharmacies can lower out-of-pocket costs.

Safety Profile

Topical anti-infective therapy is generally well-tolerated. Adverse effects are similar to other topical therapies and include irritation, dryness, burning, itching, epistaxis, post-nasal drainage, ear pain, and sore throat. There is a theoretic risk of ototoxicity and nephrotoxicity with topical aminoglycosides, although this has not been documented with irrigations. Resistance development is also a concern.⁵ In the mupirocin RCT by Jervis Bardy and Wormald,⁴¹ there was a documented case of mupirocin-resistant *S aureus*. Exacerbation of respiratory symptoms, such as asthma, has been reported with topical antifungal therapy.¹

TOPICAL ALTERNATIVE THERAPIES

Inhibitors of Biofilm Formation

Although the cause of CRS is now believed to be primarily inflammatory, infection may potentially still play a role in recalcitrant disease. The ability of pathogenic bacteria in CRS, particularly *S aureus* and *P aeruginosa*, to form biofilms, well-organized structures of bacterial communities encased in a self-produced polymeric matrix tightly adhered to the sinonasal mucosa, has been proposed to contribute to their recalcitrance.^{49,50} Several topical alternative therapies have emerged targeting these biofilms.

Surfactants

Surfactants are compounds that are hydrophobic and hydrophilic. In the orthopedic literature, chemical surfactants, such as those found in shampoos, have been shown to inhibit biofilm formation. Naturally occurring surfactants in the respiratory system also decrease the surface tension and viscosity of mucus.⁵ Given these properties, the effect of baby shampoo irrigations has been studied in the setting of CRS. Despite favorable initial pilot studies, an RCT comparing 1% baby shampoo and hypertonic

saline irrigations showed no significant differences in symptom scores between the two groups, and the baby shampoo group had a higher rate of discontinued use because of side effects, most commonly nasal irritation.⁵¹ Baby shampoo has also been shown to increase mucociliary clearance time.⁵² There is currently not enough evidence to provide recommendations regarding surfactant irrigations in CRS.⁵

Manuka honey

Manuka honey has long been used in the treatment of wounds, which are prone to bacterial biofilm formation. The mechanisms behind its ability to inhibit biofilm formation are postulated to be related to multiple properties, including its high sugar content and therefore osmolality; its acidity; its hydrogen peroxide activity; and the presence of unique phytochemical compounds, such as methylglyoxal (MGO).^{53–56} Manuka honey is also effective against a broad range of bacteria, including most relevantly *S aureus* and *P aeruginosa*.⁵⁷

Two RCTs have been performed examining manuka honey irrigations in CRS, both in the post-ESS setting on a particularly recalcitrant subset of patients. In the study by Lee and colleagues,⁵⁸ 42 patients were included in the per-protocol analysis, 20 randomized to perform manuka honey irrigations and 22 randomized to perform saline irrigations for 1 month. Both groups achieved clinically meaningful improvement in SNOT-22 scores. SNOT-22 scores, endoscopic scores, and post-treatment culture negativity rates were better in the manuka honey group compared with the saline group, but these differences were not significant. A limitation of this study was that adjunctive systemic therapies were offered at the clinician's discretion. In a subgroup analysis of patients who did not receive any adjunctive treatment, the manuka honey group achieved significantly better culture negativity rates than the saline group, suggesting that manuka honey may have microbiologic benefit and that the relative importance of systemic therapy may be higher in patients receiving saline irrigation alone.⁵⁸ In the study by Ooi and colleagues,⁵⁹ 25 patients were included in the per-protocol analysis, 15 randomized to receive manuka honey irrigations with an MGO additive and 10 randomized to receive saline and culture-directed oral antibiotics. Saline and culture-directed oral antibiotics seemed to be superior to manuka honey only in eradication of infection on culture. There were no significant differences in symptom or endoscopic scores between the groups. The study was intended as a phase 1 safety and tolerability study, and as a result, the authors state it was likely underpowered. Smell function was assessed by Ooi and colleagues⁵⁹ and unchanged with the manuka honey irrigations. The irrigations were well-tolerated, and no serious adverse effects were reported in either study.^{58,59} At higher concentrations of MGO than used in the study by Ooi and colleagues, it does become ciliotoxic.^{54,60}

In summary, these studies focused on the recalcitrant post-ESS subset of CRS suggest that manuka honey irrigations may have the greatest effect on microbiologic outcomes. There is no evidence of a symptomatic or endoscopic benefit compared with saline. These data, however, are limited with only two RCTs, one of which is underpowered. Larger prospective studies are needed to make recommendations regarding the use of these irrigations in CRS.⁵

Xylitol

Xylitol enhances the activity of innate immune factors present in respiratory secretions, eliciting a downstream bactericidal effect. There is only one small RCT with substantial participant dropout, which demonstrated a significant symptomatic benefit with xylitol irrigations.⁶¹ Further research is needed to make a recommendation regarding their use in CRS.⁵

Table 2 Summary of topical therapies in chronic rhinosinusitis				
Type	Recommended?	Formulation	Cost	Specific Safety Concerns
Saline irrigation	Yes, routine Yes, postoperative	High-volume (>200 mL)	Low (\$0.24/d)	None
Corticosteroid sprays	Yes, routine Yes, postoperative	Metered-dose solutions	Low	None
Corticosteroid irrigations	Option, mainly postoperative	Variable (eg, budesonide)	Higher (lower with compounding pharmacies)	Possible HPA axis suppression
Antibiotic irrigations	No, routine May have role in recalcitrant cases Ideally culture-directed	Highly variable	Higher (lower with compounding pharmacies)	Resistance development Ototoxicity/ nephrotoxicity (aminoglycosides)
Antifungal irrigations	No Further research needed for allergic fungal subtype	Variable (eg, amphotericin B)	Higher (lower with compounding pharmacies)	Exacerbation of respiratory conditions
Alternative therapies (surfactants, manuka honey, xylitol)	Insufficient evidence	Highly variable	Highly variable	None specifically

Probiotics: The New Frontier

In recent years, there has been an increasing focus on the commensal sinonasal microbiome and its role in the development of a functional immune system. It has been theorized that infections in CRS may be related to a decrease in diversity of the commensal microbiome and an increase in pathogenic bacteria. The concept behind the therapeutic potential of topical probiotics is that they outcompete pathogenic bacteria via a variety of mechanisms, including creating suboptimal environmental conditions, competing for cell surface receptors and thus limiting pathogen adherence, and producing antibacterial metabolites. In doing so, topical probiotics restore the commensal microbiome.

Recent research has focused on determining what constitutes this microbiome, which has proved to be a difficult task. A goal of these efforts is to better inform the selection of topical probiotics to restore it. There are little data evaluating topical probiotics in the treatment of CRS, but the data examining topical probiotics in otitis media and recurrent tonsillitis are promising and demonstrate an excellent safety profile. The therapeutic potential of topical probiotics in CRS is still in its infancy, but it is an exciting new area of research.⁶²

SUMMARY

Topical therapies allow for delivery at higher local concentrations and minimize systemic absorption, providing attractive treatment options given the accessibility of the sinonasal cavity (Table 2). Saline irrigations and topical corticosteroid sprays

are recommended in the treatment of CRS. Further research on the effect of topical corticosteroid irrigations and possible HPA axis suppression is needed to make a recommendation regarding their use, which is currently an option primarily in the post-operative setting. Topical antibiotics and antifungals are not recommended in the treatment of routine CRS but may have a role in recalcitrant CRS and AFRS, respectively. Investigations are currently underway on a variety of topical alternative therapies, with additional ones, such as topical probiotics, on the horizon.

DISCLOSURE

The author has nothing to disclose.

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