Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations

Luke Rudmik, MD[1], Monica Hoy, MD[1], Rodney J. Schlosser, MD[2], Richard J. Harvey, MD[3], Kevin C. Welch, MD[4], Valerie Lund, MD[5] and Timothy L. Smith, MD, MPH[6]

Background: **Topical therapies have become an integral component in the management plan for chronic rhinosinusitis (CRS). Several topical therapy strategies have been evaluated, but a formal comprehensive evaluation of the evidence has never been performed. The purpose of this article is to provide an evidence-based approach for the utilization of topical therapies in the management of CRS.**

Methods: **A systematic review of the literature was performed and the guidelines for development of an evidence-based review with recommendations were followed. Study inclusion criteria were: adult population >18 years old; chronic rhinosinusitis (CRS) based on published diagnostic criteria; and clearly defined primary clinical end-point. We focused on reporting higher-quality studies (level 2b or higher), but reported on lower-level studies if the topic contained insufficient evidence. We excluded drug-eluting spacer and stent therapy from this review.**

Results: **This review identified and evaluated the literature on 5 topical therapy strategies for CRS: saline irrigation, topical steroid, topical antibiotic, topical antifungal, and topical alternatives (surfactant, manuka honey, and xylitol irrigations).**

Conclusion: **Based on the available evidence, sinonasal saline irrigation and standard topical nasal steroid therapy are *recommended* in the topical treatment of CRS. Non-standard (off-label) topical sinonasal steroid therapies can be an *option* for managing CRS. The evidence *recommends against* the use of topical antifungal therapy and topical antibiotic therapy delivered using nebulized and spray techniques in routine cases of CRS. There is insufficient clinical research to provide recommendations for alternative therapies or topical antibiotic therapy delivered using other delivery methods (eg, irrigations).**

Key Words:
chronic rhinosinusitis; therapeutics; evidence-based medicine; medical therapy of chronic rhinosinusitis; topical therapy for chronic rhinosinusitis

How to Cite this Article:
Rudmik L, Hoy M, Schlosser RJ, et al. Topical therapies in the management of chronic rhinosinusitis: an evidence-based review with recommendations. *Int Forum Allergy Rhinol*. 2012; 00:X-XX.

[1]*Endoscopic Sinus and Skull Base Surgery, Division of Otolaryngology–Head and Neck Surgery, Department of Surgery, University of Calgary, Calgary, Alberta, Canada;* [2]*Division of Rhinology and Sinus Surgery, Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston, SC;* [3]*Rhinology and Sinus Surgery, Applied Medical Research Center St Vincents Hospital, University of New South Wales and Macquarie University, Sydney, Australia;* [4]*Department of Otolaryngology–Head and Neck Surgery, Loyola University Medical Center, Maywood, IL;* [5]*Professional Unit, Royal National Throat Nose and Ear Hospital, London, UK;* [6]*Division of Rhinology and Sinus Surgery, Department of Otolaryngology–Head and Neck Surgery, Oregon Health and Science University, Portland, OR*

Correspondence to: Luke Rudmik, MD, University of Calgary, Otolaryngology–Head and Neck Surgery, Foothills Medical Centre Suite 602, South Tower 1403 - 29st NW, Calgary, Alberta T2N 2T9, Canada; e-mail: lukerudmik@gmail.com

Potential conflict of interest: There were no direct financial costs related to the development of this manuscript. All incoming authors disclosed their conflicts of interest and they are reported in this manuscript. This manuscript was not discussed with industry prior to publication.

Treatment of chronic rhinosinusitis (CRS) is primarily focused on reducing mucosal inflammation, removing bacterial infection/colonization, and improving sinonasal function. To minimize the potential for adverse effects, clinicians often try to minimize systemic medical therapies and favor the use of topical therapies to focus drug delivery locally. Advantages of topical medical therapy include direct drug delivery onto diseased tissue, potential for delivering higher local drug concentrations, and minimizing systemic absorption. Disadvantages of topical medical therapy include challenges with application technique, local adverse effects (eg, epistaxis or discomfort), and variable sinus penetration. Due to the accessible nature of the sinonasal cavity, it is very amenable to topical medical therapy and has

Received: 5 April 2012; Revised: 27 June 2012; Accepted: 21 July 2012
DOI: 10.1002/alr.21096
View this article online at wileyonlinelibrary.com.

TABLE 1. Review characteristics

Purpose • Outline the evidence evaluating topical nasal and sinonasal medical therapies for the management of CRS • Promote an evidence-based strategy for topical therapy management of CRS.
Goal • Provide focused summaries and, when possible, recommendations for specific topical therapies in order to assist clinicians with optimizing management for CRS. CRS is a very heterogeneous disease and these evidence-based recommendations should not necessarily be applied to all patients and clinician judgment, in addition to the evidence, is critical to determining the most appropriate care.
Focus • Disease: chronic rhinosinusitis with and without nasal polyps • Population: adults >18 years old • Intervention: topical sinonasal medical therapies
Intended users • Clinicians who care for patients with CRS

CRS = chronic rhinosinusitis.

become an integral drug-delivery strategy in the management of CRS.

Effective drug delivery to the involved tissue is a challenge that all topical drug therapies must overcome during the management of CRS. Endoscopic sinus surgery (ESS) is an important component in the management of medically refractory CRS, both clinically[1] and economically.[2] One major advantage of ESS is creating an open and accessible cavity, which has been demonstrated to optimize sinonasal penetration of topical medical therapy.[3] Since the majority of patients following ESS will require ongoing medical therapy to control inflammatory disease, the creation of an open sinus cavity has become a critical component to improve topical drug delivery and provide long-term clinical success. The interaction of delivery technique, prior sinus surgery, and extent, along with the pharmacokinetics of topical sinonasal irrigation, has not been addressed specifically and may warrant a separate review. The active agent is the focus of this review.

Topical sinonasal medical therapy is thought to be an important strategy in the management of CRS and a formal evidence-based review with practice recommendations is required to guide patients and physicians in treatment options. The purpose of this review is to identify topical medical therapy strategies and promote an evidence-based approach to their use (Table 1). For each topical medical therapy strategy, this review provides a focused summary of the literature and when possible, recommendations are introduced based on the supporting evidence and value judgments made by the authors.[4] This review is not intended to replace professional judgment, rather it is meant to assist clinicians with understanding the available evidence and the potential tradeoffs associated with each topical treatment strategy.

Methods

The overall development of this manuscript was performed by following the published methodology for an evidence-based review with recommendations.[4] We defined topical medical therapy as the application of a therapeutic agent directly into the sinonasal cavity. A systematic review of the literature was performed using Medline, EMBASE, and Cochrane Review Databases up to January 15, 2012. A screening literature search, which was used to identify all topical medical therapies reported for CRS, was performed using keywords: "chronic," "$sinusitis," and "$topical." The resulting 267 abstracts were evaluated and 5 potential topical medical therapy strategies were identified (Table 2).

A second focused literature search for each individual strategy listed in Table 2 was performed using the keywords: "chronic," "$sinus," and each of the 5 strategies from Table 2 (ie, "topical saline irrigations," "topical corticosteroids," "topical antibiotics," "topical antifungals,"), for a total of 5 searches. In addition, reference lists of all identified studies were examined and we contacted experts in this field of research to ensure all in-press studies were captured. All abstracts were reviewed and the following study inclusion criteria were applied: Adult population >18 years old; chronic rhinosinusitis based on published

TABLE 2. Potential topical sinonasal therapy strategies

Topical saline irrigations
Topical corticosteroids
Topical antibiotics
Topical antifungals
Topical alternatives

TABLE 3. Defined grades of evidence*

Grade	Research quality
A	Well-designed RCTs
B	RCT with minor limitations; overwhelming consistent evidence from observational studies
C	Observational studies (case control and cohort design)
D	Expert opinion; case reports; reasoning from first principles

*American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM).[8]
RCT = randomized controlled trial.

diagnostic criteria[5,6]; primary study objective was to evaluate a defined topical medical therapy; and clearly defined primary clinical end-point. We focused on reporting higher-quality studies (level 2b or higher), but reported on lower-level studies if the topic contained insufficient evidence. We excluded studies that included the following in the overall study cohort: pediatric patients (age <18 years old) and non-CRS disease (eg, allergic rhinitis). Exclusion criteria included drug-eluting spacer and stent therapy.

Included studies were evaluated and level of evidence was applied based on reported research methodology.[7] After quality evaluation for each study, a summary was produced that includes the aggregate grade of evidence (Table 3) and recommendations based on the American Academy of Pediatrics (AAP) guidelines (Table 4).[8] When there was only a single study evaluating a topical medical therapy strategy, an aggregate grade of evidence was not provided because grades are derived from the findings of multiple studies. Two authors (L.R. and M.H.) reviewed the literature and produced the initial manuscript. One at a time, subsequent authors (T.L.S., R.J.S., R.J.H., K.C.W., V.L.) were asked to review and critically appraise the recommendations based on the literature. The online iterative process of review and recommendation development was performed by following the strategy outlined by Rudmik and Smith.[4] Recommendations incorporate both the quality of research methodology and the balance of benefit vs harm. Due to significant dose- and treatment-frequency variation in topical therapy strategies, we are unable to provide exact direct costs. We provide an estimated direct cost for each medication based on reported U.S. market values (June 2012) and the average daily cost was estimated based on the most commonly reported dosing schedule for each medication (Table 5). The reported costs do not reflect "out of pocket" costs to the patient because these will vary significantly depending on the patient's insurance plan.

Results: Topical therapies in the management of CRS

Sinonasal saline irrigations

Nasal saline irrigation is a common treatment adjunct in the management of CRS. The favorable safety profile, lack of systemic absorption risk, and good patient acceptance make it an appealing long-term topical therapy strategy.[9] Although irrigation solutions often include either isotonic or hypertonic saline, there is substantial variability in the volume (low or high), pressure (low or high), and frequency (once daily to 4 times daily) of saline irrigation protocols. Adverse effects of saline irrigations are rare, but include local irritation, ear pain, nosebleeds, headache, nasal burning, and nasal drainage.[10]

This review identified 8 randomized controlled (RCT) studies (5 presurgical; 3 post-ESS)[10–17] and 1 meta-analysis[18] evaluating the impact of nasal saline irrigations on clinical outcomes in adult CRS (Table 6). All 5 presurgical RCTs demonstrated that sinonasal saline irrigations improve symptom and health-related quality of life (HRQoL) outcomes in patients with CRS. The randomized trials by Bachmann et al.[11] and Hauptman and Ryan[14] evaluated the effects of isotonic and hypertonic saline irrigations and demonstrated that both solutions improve sinonasal symptoms, while there were no significant differences between groups. The study by Rabago et al.[10] randomized patients into 2 groups (hypertonic saline irrigations and no treatment) and evaluated CRS HRQoL, general QoL, symptom scores, and medication usage. The results demonstrated that daily hypertonic nasal saline irrigations significantly improved CRS HRQoL, symptom scores, and decreased medication usage. However, there was no difference in the general QoL outcomes using the 12-Item Short Form Health Survey (SF-12) questionnaire.[10] The randomized trial by Heatley et al.[12] compared isotonic nasal saline irrigations to reflexology as a control. The results

TABLE 4. Recommendations based on defined grades of evidence*

Grade	Research quality	Preponderance of benefit over harm	Balance of benefit and harm
A	Well-designed RCTs	Strong recommendation	Option
B	RCT with minor limitations; overwhelming consistent evidence from observational studies	Strong recommendation/recommendation	Option
C	Observational studies (case control and cohort design)	Recommendation	Option
D	Expert opinion; case reports; reasoning from first principles	Option	No recommendation

*American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM).[8]
RCT = randomized controlled trial.

TABLE 5. Estimated topical sinonasal medication costs

Medication	Unit	Estimated market cost per unit ($)	Estimated per day cost ($)
Neilmed saline sinus rinse bottle	1 box with 50 salt packages	11.99	0.24
Mometasone furoate (Nasonex)	17-g bottle	134.40	4.48
Fluticasone propionate (generic)	16-g bottle	18.31	0.61
Fluticasone propionate (Flonase)	16-g bottle	92.31	3.08
Fluticasone furoate (Veramyst)	10-g bottle	114.82	3.83
Budesonide (Rhinocort)	9-g bottle	121.58	4.05
Ciclesonide (Omnaris)	12.5-g bottle	42.00	1.40
Beclomethasone dipropionate monohydrate	25-g bottle	144.00	4.80
Flunisolide (Nasalide)	25-mL bottle	65.22	2.17
Triamcinolone acetonide (Generic)	17-g bottle	81.91	2.73
Triamcinolone acetonide (Nasocort)	17-g bottle	124.51	4.15
Budesonide respule (0.5 mg/2 mL)	1 respule	4.19	4.19
Budesonide respule (1 mg/2 mL)	1 respule	4.97	4.97
Prednisolone 1% drop	15-mL bottle	42.14	2.81
Ciprofloxacin-dexamethasone (0.3/0.1%) drop	8-mL bottle	157.93	10.51
Dexamethasone 0.1% drop	15-mL bottle	78.07	5.20
Mupirocin 2% ointment	22-g tube	18.62	2.66
Nebulized tobramycin	5 mL	7.64	7.64

demonstrated that all groups received CRS HRQoL improvements; however, there were no differences between the reflexology and saline irrigation groups. The randomized trial by Pynnonen et al.[15] compared high-volume (240 mL) low-pressure isotonic saline irrigation to low-volume nasal saline spray and evaluated HRQoL (20-item Sino-Nasal Outcomes Test [SNOT-20]) and symptom scores at 2, 4, and 8 weeks posttreatment. The results demonstrated that both groups received improvement in HRQoL at 8 weeks; however, there was a significantly better improvement in both HRQoL and symptoms in patients using high-volume saline irrigations.[15]

When evaluating postoperative outcomes, 2 of the 3 studies demonstrated improved symptom scores with saline irrigations.[16,17] The level 1b study by Liang et al.[17] compared saline irrigations combined with postoperative debridement to debridement alone. The results demonstrated normal saline (NS) irrigations combined with sinus debridement significantly improved both patient symptoms and endoscopic appearance in the mild CRS patient cohort, whereas the addition of NS irrigation to sinus debridement failed to demonstrate any improvement in the moderate-severe CRS group. The level 2b study by Freeman et al.[16] demonstrated that normal saline irrigations improved early (3 weeks) endoscopic appearance and mucociliary function; however, there was minimal difference at 3 months after the ESS procedure.[16] One disadvantage of this study was the use of a low-volume saline irrigation protocol (2 mL atomized). Conclusions from this study cannot be directly applied to patients who use a common high-volume (240 mL) nasal saline irrigation protocol. The study by Pinto et al.[13] evaluated symptom outcomes for a 30-mL 4-times-daily irrigation protocol using normal saline, hypertonic saline, or no irrigation. The results demonstrated no difference in patient symptom scores between groups, whereas hypertonic saline increased nasal drainage and pain.

The systematic review and meta-analysis (level 1a) by Harvey et al.[18] included 8 studies that evaluated the following designs: saline vs no treatment; saline vs placebo; saline as an adjunct to intranasal steroid (INS) therapy; saline vs INS therapy; and isotonic vs hypertonic saline irrigations. A few studies included pediatric patients with CRS, and allergic rhinitis. The results demonstrated that saline irrigations improve symptom outcomes when used as the sole CRS treatment modality; however, saline was demonstrated to be less effective compared to INS therapy.

TABLE 6. Summary of topical sinonasal saline irrigation studies

Study	Year	Study design	LOE	No. of Subjects	Study groups	Treatment protocol	Primary clinical end-points	Conclusion
Bachmann et al.[11]	2000	RCT no blinding	2b	40	1) Hypertonic saline; 2) Isotonic saline	200 mL BID intranasal irrigation × 1 week	1) Symptoms; 2) Endoscopy; 3) Mucociliary clearance; 4) Rhinomanometry; 5) Olfactometry	No difference between hypertonic and isotonic
Heatley et al.[12]	2001	RCT; no blinding	2b	150	1) Isotonic saline in bulb syringe; 2) Isotonic saline in pot irrigation; 3) Reflexology as placebo	Unspecified volumes daily × 2 weeks	1) HRQoL (RSOM31, SNOT20); 2) QoL (SF-36)	All groups had improvement ins RSOM31 and SNOT20 scores. No difference between saline group and reflexology
Rabago et al.[10]	2002	RCT; no placebo; no blinding	2b	76	1) Isotonic saline; 2) No treatment	Daily × 6 months 3) Severity assessment (SIA score)	1) HRQoL (RSDI); 2) QoL (SF-12); 3) Severity assessment (SIA score)	Improved RSDI and SIA scores. No improvement in SF-12.
Pinto et al.[13]	2006	RCT	2b	60	1) Normal Saline (NS) 2) Hypertonic Saline (HS) 3) No irrigations	Began POD 1; 30 mL 4× daily	1) Symptoms	No difference in postoperative symptoms between NS and no irrigation. HS produces worse pain and nasal drainage
Hauptman and Ryan[14]	2007	RCT; double-blind	1b	80	1) Isotonic saline; 2) Hypertonic saline	1 mL of solution administered through a nasal spray bottle to more symptomatic side of nose 3) Saccharine clearance	1) Symptoms; 2) Acoustic rhinometry; 3) Searcharine clearance	NSand HS improved symptoms of nasal stuffiness and obstruction. NS improved nasal airway patency.
Pynnonen et al.[15]	2007	RCT	1b	121	1) High volume (240 mL) low pressure isotonic saline irrigation; 2) Isotonic saline spray	BID treatment × 8 weeks	1) HRQoL (SNOT-20); 2) Symptom	Significant HRQoL improvement in both groups. High-volume low-pressure irrigation group received more HRQoL and symptom improvement compared to low-volume spray group.
Harvey et al.[18]	2007	Meta-analysis	1a	8 trials included. Some trials included both pediatric patients and patients with allergic rhinitis.	1) Saline irrigations vs. No Treatment OR placebo OR adjunct to other treatment; 2) Isotonic vs. Hypertonic saline	Variable	1) Symptom (all); 2) Radiologic (only for isotonic vs hypertonic)	Saline irrigations improve symptoms of CRS when used as a sole modality. Saline may improve symptoms when used as an adjunct with intranasal steroids. Saline is not as effective as compared to an intranasal steroid. Little evidence to support a difference in outcomes between hypertonic and isotonic saline irrigations
Freeman et al.[16]	2008	RCT	2b	23	1) NS 2) No irrigations	Began POD1; Atomization of 2 mL 3× daily	1) Endoscopy	NS provided early endoscopic improvement (reduced discharge and edema). No difference in long-term endoscopic findings (adhesions, crusting, polyps).
Liang et al.[17]	2008	RCT	1b	77	1) NS + debridement; 2) Debridement alone	Began POD1; 240 mL 1× daily	1) Symptom; 2) Endoscopy	NS group, with mild CRS, had better symptom and endoscopy scores. No difference in patients with moderate-severe CRS.

BID = twice daily; CRS = chronic rhinosinusitis; HRQoL = health related quality of life; HS = hypertonic saline; LOE = level of evidence; NS = normal saline; POD = postoperative day; QoL = quality of life; RCT = randomized controlled trial; RSDI = Rhinosinusitis Severity Disability Index; RSOM = Rhinosinusitis Outcome Measure; SF = Short Form; SIA = Single-item Sinus-symptom Severity Assessment; SNOT = Sinonasal Outcome Test.

There is evidence that saline can improve symptoms when used as an adjunct to INS therapy. Isotonic and hypertonic saline solutions appear to have similar effects on patient symptoms and HRQoL; however, hypertonic solutions may improve objective outcomes, such as radiographic imaging.

There is substantial evidence to support the use of sinonasal saline irrigations in the management of CRS. Due to the excellent safety profile of sinonasal saline irrigations, there is a preponderance of benefit over harm and, when combined with an aggregate grade B of evidence, we have provided a recommendation for its use in the management of CRS. Although sinonasal saline irrigations can improve symptom and HRQoL outcomes in patients with CRS, it is important to recognize that it is often implemented as an adjunct to other topical therapy strategies. Isotonic and hypertonic saline irrigations appear to provide similar subjective outcomes, and high-volume low-pressure saline irrigation appears to be superior to low-volume nasal saline spray therapy.

Summary: Topical sinonasal saline irrigations

Aggregate quality of evidence. B (Level 1a: 1 study; Level 1b: 2 studies; Level 2b: 5 studies—heterogeneity of methods and outcomes prevent A).

Benefit. Improved HRQoL, symptom, endoscopic, and radiologic outcomes. Well tolerated. No risk of systemic adverse effects.

Harm. Local irritation, sinonasal burning, headaches, and ear pain/congestion.

Cost. Minimal ($0.24/day); patient time for application.

Benefits-harm assessment. Preponderance of benefit over harm.

Value judgments. Important to use sinonasal saline irrigation as an adjunct to other topical therapy strategies. Higher-volume (≥200 mL) irrigations appear to be superior to low-volume nasal sprays but no recommendation on optimal frequency can be made.

Recommendation level. Recommendation.

Intervention. Use sinonasal saline irrigations as an adjunct to other medical therapies for CRS.

Topical sinonasal steroids

Use of topical sinonasal steroid therapy can achieve local steroid effects while minimizing potential adverse effects associated with systemic steroid therapy. Due to the localized anti-inflammatory effects and excellent safety profile, topical sinonasal steroid therapy has become a common treatment modality for CRS. There are several potential topical steroid solutions and this article categorizes them into "standard" and "nonstandard" therapies. Standard therapies pertain to metered-dose topical steroid solutions that have been approved for *nasal* use by the U.S. Food and Drug Administration (FDA). The FDA-approved topical nasal steroid agents include metered-dose nasal spray delivery of the following: mometasone furoate, fluticasone propionate, fluticasone furoate, budesonide, beclomethasone dipropionate monohydrate, ciclesonide, flunisolide, and triamcinolone acetonide (see Table 7 for FDA approved indications). Nonstandard topical steroid therapies lack specific FDA approval for *nasal* therapy and are utilized in an "off-label" indication. Potential side effects of topical steroid therapy occur in <5% of patients and most commonly include headache, epistaxis, and cough.[19] Although there is a breadth of evidence on standard topical steroid therapies, there is a growing body of evidence for the use of nonstandard, off-label sinonasal steroid solutions. Advantages of nonstandard steroid solutions include delivery of higher volume and higher concentrations of topical steroid to the sinonasal mucosa. The predominant risk of nonstandard topical sinonasal steroid therapy is the potential systemic absorption, resulting in the side effects associated with systemic steroid therapy.

Standard therapies

This review identified 5 meta-analyses evaluating the role of standard topical nasal steroid therapy on clinical outcomes for both CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP) (Table 8).[20–24] All studies were level 1a quality and 4 demonstrated significant improvement in both objective (endoscopic) and subjective (symptom) clinical outcomes. The studies by Joe et al.,[20] Rudmik et al.,[22] and Snidvongs et al.[24] evaluated the effect of topical steroid therapy in patients with nasal polyposis. Joe et al.[20] combined the data from 6 RCTs that evaluated the treatment effect on objective size of NP. Using a 4-point polyp-size grading system, the results demonstrated a significant reduction in polyp size of 0.43 for the conservative overall estimates (95% confidence interval [CI], 0.25–0.61) and the highest overall estimates of 0.63 reduction (95% CI, 0.43-0.82). Because a reduction in polyp size is only a surrogate for clinical improvement, the recent study by Rudmik et al.[22] combined the data from 12 RCTs to determine the treatment effect on patient symptoms. Studies that reported a discrete (success vs failure) symptom-specific outcome were included in the quantitative meta-analysis. The pooled risk ratio of successful improvement in patient symptoms was 1.72 (95%CI, 1.41–2.09), which demonstrates a significant symptom improvement with topical nasal steroid therapy in patients with CRSwNP. Similarly, the study by Snidvongs et al.[24] demonstrated that topical

TABLE 7. FDA-approved indications for standard topical nasal steroid therapies

Generic steroid agent	Trade name	Delivery	FDA-approved indications
Mometasone furoate	Nasonex	Low-volume spray	1) Seasonal and perennial allergic rhinitis in patients >2 years old; 2) Prophylaxis of seasonal allergic rhinitis in patients >12 years old; 3) CRSwNP in patients >18 years old
Fluticasone propionate	Flonase	Low-volume spray	1) Seasonal and perennial allergic rhinitis in patients >4 years old; 2) Non-allergic rhinitis in patients >4 years old
Fluticasone furoate	Veramyst	Low-volume spray	Seasonal and perennial allergic rhinitis in patients >2 years old
Budesonide	Rhinocort	Low-volume spray	Seasonal and perennial allergic rhinitis in patients >6 years old
Ciclesonide	Omnaris	Low-volume spray	Seasonal and perennial allergic rhinitis in patients >12 years old
Beclomethasone dipropionate monohydrate	Beconase	Low-volume spray	1) Seasonal and allergic rhinitis in adults; 2) CRSwNP in adults
Flunisolide	Nasalide	Low-volume spray	Seasonal and perennial allergic rhinitis
Triamcinolone acetonide	Nasacort	Low-volume spray	Seasonal and perennial allergic rhinitis in patients >2 years old

CRSwNP = chronic rhinosinusitis with nasal polyposis; FDA = U.S. Food and Drug Administration.

steroid therapy for CRSwNP resulted in improved symptom scores (standardized mean difference [SMD] −0.46; 95% CI, −0.65 to −0.27), $p < 0.00001$, 7 trials, 445 patients) and a higher proportion of responders. Reduction in polyp scores and improvements in nasal peak inspiratory flow rates were also recorded. On subgroup analysis, patients with sinus surgery responded to topical steroid more than patients without sinus surgery in polyp size reduction.

The studies by Kalish et al.[21] and Snidvongs et al.[23] evaluated the effect of topical steroid therapy in patients with CRSsNP. Kalish et al.[21] combined the results from 6 RCTs and concluded that there was insufficient evidence to demonstrate a significant overall response to treatment using topical steroids in CRSsNP. However, when combining the total symptom scores from 3 trials, the standardized mean improvement favored topical steroid therapy (RR 0.63; 95% CI, 0.16-1.09), suggesting there may be a total symptom benefit. The recent study by Snidvongs et al.[23] combined the results from 10 RCTs and demonstrated that topical steroid therapy results in improved overall symptom scores (SMD −0.37; 95% CI, −0.60 to −0.13) and a higher proportion of symptom responders. A subgroup analysis demonstrated a greater symptom improvement with direct sinus delivery of topical steroid compared to simple nasal delivery.

There is overwhelming evidence from 5 meta-analyses that standard topical steroid therapy results in both patient-based and objective clinical improvements in CRSwNP and CRSsNP. When combining an aggregate grade A of evidence with a preponderance of benefit over harm, we have produced a strong recommendation for the use of standard topical steroid therapy in patients with CRS. To optimize treatment effect, the evidence suggests that the delivery technique should focus on improving sinus penetration rather than simple nasal application.

Summary: Standard topical nasal steroid spray

Aggregate quality of evidence. A (Level 1a: 5 studies).

Benefit. Improved symptoms and endoscopic appearance. Reduced polyp size.

Harm. Headache. Epistaxis. Cough.

Cost. Low to moderate (range, $0.61/day to $4.80/day); depends on preparation.

Benefits-harm assessment. Preponderance of benefit over harm.

Value judgments. The authors recognize that other topical therapy options may be required when an adequate

TABLE 8. Summary of standard topical nasal steroid studies

Study	Year	Study design	LOE	Studies included (n)	Study groups	Treatment protocol	Primary clinical end-point	Conclusion
Joe et al.[20]	2008	Meta-analysis	1a	6 RCTs	CRSwNP	Topical INS therapy	Polyp size	INS decrease the objective size of NPs on endoscopy
Kalish et al.[21]	2009	Meta-analysis	1a	9 RCTs	CRSsNP	Topical INS therapy	1) Overall response to treatment; 2) Symptom	Insufficient evidence to demonstrate a clear overall benefit of topical steroid therapy in CRSsNP; may improve total symptom scores
Snidvongs et al.[23]	2011	Meta-analysis	1a	10 RCTs (n = 590)	CRSsNP	Topical INS therapy	Symptom	Topical steroid therapy improved symptoms in patients with CRSsNP; no difference in QoL or adverse events; direct deliver of topical steroid into the sinuses was more beneficial than simple nasal delivery
Rudmik et al.[22]	2012	Meta-analysis	1a	12 RCTs	CRSwNP	Topical INS therapy	Symptom	INS improve nasal symptoms in CRSwNP when compared to placebo
Snidvongs et al.[24]	in press	Meta-analysis	1a	38 RCTs	CRSwNP	Topical INS therapy	Symptom	Topical steroid therapy improved symptoms, polyp scores, and objective measures of nasal airflow

CRS = chronic rhinosinusitis; CRSsNP = CRS without NP; CRSwNP = CRS with NP; INS = intranasal steroid; LOE = level of evidence; NP = nasal polyposis; QoL = quality of life; RCT = randomized controlled trial.

International Forum of Allergy & Rhinology

trial of standard metered dose topical nasal steroid spray has failed to improve clinical outcomes.

Recommendation level. Strong recommendation—for routine cases of CRS.

Intervention. Use standard metered dose topical nasal steroid spray for routine cases of CRS.

Nonstandard therapies (ie, off-label)

Nonstandard, off-label topical steroid therapy has the theoretic advantages of delivering higher volume and concentration of steroid to the sinonasal mucosa, depending upon delivery method. Common high-volume solutions include budesonide sinonasal irrigations (0.25 mg/2 mL or 0.5 mg/2 mL in 240 mL saline), whereas low-volume solutions include intranasal dexamethasone ophthalmic drops (0.1%), prednisolone ophthalmic drops (1%), and ciprofloxacin/dexamethasone otic drops (0.3/0.1%).

This review identified 6 studies evaluating nonstandard topical steroid therapy in the management of CRS (Table 9).[25–28] The highest-quality study by Rotenberg et al.[26] is the only RCT (level 1b) evaluating the clinical effects of an off-label steroid solution in patients with CRS. They evaluated the effect of budesonide sinonasal irrigations on both patient-based (HRQoL) and objective (radiographic and endoscopic) clinical outcomes in patients with Samter's triad who underwent ESS. Three postoperative treatment groups included saline irrigation alone, budesonide nasal spray, and budesonide saline irrigations. All groups received significant postoperative outcome improvements; however, there was no difference in outcomes between groups. Although this study demonstrated no positive clinical effect of an off-label topical steroid therapy, it is important to evaluate the findings in the context of patients with Samter's triad.

Due to the paucity of literature on this topic, we included 5 level 4 studies in the discussion.[25,27–30] A retrospective study by DelGaudio et al.[25] evaluated intranasal dexamethasone ophthalmic drops (0.1%), prednisolone ophthalmic drops (1%), and ciprofloxacin/dexamethasone otic drops (0.3/0.1%) in patients who underwent revision ESS with a high risk for sinus ostial stenosis and polyp recurrence. They concluded that nonstandard, high-dose nasal steroid drops might reduce sinus ostial stenosis, need for revision sinus surgery, and reduce oral steroid rescue episodes. In 2008, a case series by Kanowitz et al.[30] evaluated post-ESS topical budesonide delivered using a mucosal atomization device (MAD). With a mean follow-up of 31 months, they demonstrated a reduced need for systemic steroids along with improved patient and physician global assessment scores.[30] A small prospective trial by Sachanandani et al.[29] evaluated 9 patients undergoing topical budesonide therapy (0.25 mg diluted in 5 mL of isotonic saline) and demonstrated improved disease-specific QoL (SNOT-20) with no alterations in adrenal cortex function. The study by Steinke et al.[27] was a small, uncontrolled prospective pilot study (8 patients) that evaluated both patient-related and objective outcomes for hyperplastic CRS. They demonstrated that high-volume budesonide sinonasal saline irrigations may improve both patient-based symptom scores and objective measures (CT and endoscopy). A recent large series by Snidvongs et al.[26] evaluated 111 patients receiving large-volume saline irrigation combined with either budesonide 1 mg or betamethasone 1 mg following ESS. The results demonstrated that significant tissue eosinophilia did not prevent comparable improvement in SNOT-22, symptom scores, and endoscopic grades in patients using high-volume corticosteroid therapy.

There is a fear of unwanted systemic steroid absorption when using off-label higher-concentration topical steroid therapy; however, several studies have demonstrated a lack of systemic effects. The study by DelGaudio et al.[25] reported that only 1 of 36 patients required medication discontinuation due to a drop in morning cortisol level. Additionally, a study by Bhalla et al.[31] evaluating the safety of off-label topical budesonide irrigations demonstrated no significant adrenal suppression. A recent study by Welch et al.[32] demonstrated that twice daily budesonide nasal irrigations following ESS (0.5 mg/2 mL in 240 mL saline) did not alter the serum cortisol or 24-hour urine cortisol levels. Given that high-volume delivery techniques, such as squeeze bottle or Neti pot, result in less than 5% of the solution remaining in the sinuses, the actual concentration of steroid the patient is exposed to is quite low and, in fact, may be lower than traditional nasal steroid sprays.[3] Although it appears that short-term use is likely safe, future studies will need to assess the safety of long-term off-label topical nasal steroid preparations. The monetary costs of off-label steroid solutions can vary depending on concentration, volume, and frequency of application. Budesonide irrigations tend to be on the higher side of the cost spectrum due to the lack of a generic formulation option; however, the patent will expire in September 2012. This will likely result in a significant cost reduction for budesonide topical sinonasal therapy.

Although there are several potential advantages of off-label topical steroid solutions, more research is required before we can recommend this strategy for routine use. Several studies have demonstrated that off-label topical steroid therapy is safe in the short-term and therefore we feel there is a balance of benefit and harm which makes it an option in the management of CRS.

Summary: nonstandard, off-label topical sinonasal steroid therapy

Aggregate quality of evidence. C (Level 1b: 1 study; Level 4: 5 studies).

TABLE 9. Summary of nonstandard topical sinonasal steroid studies

Study	Year	Study design	LOE	No. of patients included	Study groups	Treatment protocol	Primary clinical end-point	Conclusion
DelGaudio et al.[25]	2006	Retrospective	4	36	CRS with and without polyposis following ESS. High risk for ostial stenosis or revision ESS.	Steroid nasal drops: 1) Dexamethasone ophthalmic; 2) Prednisolone ophthalmic; 3) Ciprofloxacin/ dexamethasone	1) Ostial patency; 2) Oral steroid rescue episodes; 3) Revision sinus; surgery	Topical nasal drops may reduce sinus ostial stenosis and decreased the need for revision ESS. Topical nasal drops may reduce oral steroid rescue episodes.
Kanowitz et al.[30]	2008	Retrospective	4	44	CRS with and without polyposis	1 mL of (0.5/2 mL) budesonide into each nostril BID using the MAD	1) Symptoms; 2) Endoscopy; 3) Oral steroid use; 4) Global assessment; 5) Olfaction	Topical budesonide delivered using the MAD may reduce the need for systemic steroids and improve overall global assessment.
Steinke et al.[27]	2009	Prospective pilot	4	8	CRS: chronic hyperplastic and ASA-sensitive	Topical budesonide high volume saline irrigations × 3 months	1) Radiologic (CT score); 2) Symptoms; 3) Endoscopy	Budesonide may improve patient symptoms and objective outcomes (CT score and endoscopy).
Sachanandani et al.[29]	2009	Prospective pilot	4	9	CRS with and without polyposis	0.25 mg budesonide diluted into 5 mL of isotonic saline each nostril QD	1) Adrenal function outcomes; 2) HRQoL (SNOT-20)	Topical budesonide improved SNOT-20 scores and did not affect adrenal function.
Rotenberg et al.[26]	2011	RCT; double-blind; placebo controlled	1b	60	CRS with polyposis (Samter's triad)	1) Topical high-volume budesonide saline irrigation; 2) Saline irrigation + separate budesonide nasal spray; 3) Saline alone	1) HRQoL (SNOT-20); 2) Radiologic (CT score);	No difference between study groups.
Snidvongs et al.[24]	in press	Prospective	4	111	CRSwNP, CRSsNP–all postsurgery	Budesonide or beclomethasone in high-volume irrigation	1) HRQoL (SNOT22); 2) Symptoms; 3) Endoscopy	Patients with marked tissue eosinophilia performed as well or better than other subgroups.

ASA = aspirin; BID = twice per day; CRS = chronic rhinosinusitis; CRSsNP = CRS without NP; CRSwNP = CRS with NP; CT = computed tomography; ESS = endoscopic sinus surgery; HRQoL = health-related quality of life; INS = intranasal steroid; LOE = level of evidence; MAD = mucosal atomization device; NP = nasal polyposis; QD = once per day; RCT = randomized controlled trial; SNOT = Sinonasal Outcome Test.

Benefit. Potentially reduce risk of ostial stenosis. May reduce systemic steroid rescue episodes. Potential alternative to systemic steroids.

Harm. Poorly defined risks. Potential adrenal suppression, ocular absorption, wound healing, and other systemic steroid effects.

Cost. Moderate to high (range, $4.19 to $10.51), depends on preparation and dosing schedule.

Benefits-harm assessment. Equal balance of benefit to harm.

Value judgments. Challenging to provide a recommendation for or against the use of off-label topical sinonasal steroid therapy based on 1 level 1b study that demonstrated no benefit in a highly select CRS cohort (Samter's triad), whereas 5 level 4 studies suggested there may be a clinical benefit. Great preference for topical sinonasal steroid therapy vs systemic steroid therapy.

Recommendation level. Option—in cases of CRS.

Topical sinonasal antibiotics

The extent to which bacterial colonization, infection, and biofilm contribute to the pathophysiology of CRS is controversial. Systemic antibiotics are typically reserved for treatment of acute exacerbations of CRS; however, some evidence suggests that long-term macrolide therapy can improve both subjective and objective outcomes while providing both anti-inflammatory and prociliary benefits in addition to the antimicrobial effects.[33,34] Potential adverse effects of systemic antibiotics include gastrointestinal symptoms (cramping and diarrhea), *Clostridium difficile* colitis, anaphylaxis, and increased bacterial resistance. Topical antibiotic therapy attempts to deliver a higher concentration of antibiotic to the site of infection while reducing the risk of systemic adverse effects. Several studies have evaluated the role of topical antibiotic therapy in the management of CRS.

This review identified 3 RCTs[35–37] and 1 systematic review[38] evaluating the role of topical antibiotics in management of CRS (Table 10). All studies evaluated patients with persistent symptoms who underwent ESS and incorporated both a placebo and double-blind methodology. However, all studies were small, evaluated different topical antibiotics and used different application techniques.

The largest RCT trial by Sykes et al.[35] evaluated 2 different topical therapy agents (dexamethasone/tramazoline; neomycin/dexamethasone) compared to a placebo and used a 4 times daily spray technique. The results demonstrated that both treatment groups improved clinical outcomes compared to the placebo; however, the addition of neomycin provided no difference. The study by Desrosiers et al.[36] evaluated a tobramycin-saline solution delivered using a large-particle nebulizer compared to saline alone. After a 4-week treatment course, the results demonstrated that both groups received clinical improvement, whereas there was no additional benefit of tobramycin. The most recent study by Videler et al.[37] evaluated a protocol which included a Rhinoflow nebulizer of bacitracin/colimycin compared to placebo, and both groups received a course of levofloxacin. The results once again demonstrated that both groups received clinical improvement, whereas the topical antibiotic group failed to offer any additional clinical benefit.

The systematic review by Lim et al.[38] evaluated the evidence on topical "antimicrobial" treatments for the management of CRS that included both antibiotic and antifungal therapies. There was a large volume of lower quality research (level 3 and 4) evaluating topical antibiotics and the results from these nonrandomized uncontrolled studies demonstrated a positive impact on clinical outcomes.[39–42] However, when evaluating the higher-quality evidence (Level 1b and 2b), there appears to be limited benefit of topical antibiotic therapy when compared to placebo.

Topical high-volume mupirocin-saline irrigation has been investigated as a potential therapeutic option for patients with *Staphylococcus aureus* (*S. aureus*) culture-positive refractory CRS. A study by Le et al.[43] utilized a sheep model to evaluate multiple potential biofilm-cidal agents. They demonstrated that twice-daily mupirocin irrigations for 5 days significantly reduced preformed biofilm burden.[43] In 2008, a small prospective pilot study by Uren et al.[44] evaluated the effects of a twice-daily 0.05% mupirocin saline irrigation for 3 weeks in patients with *S. aureus*–positive refractory CRS. The results demonstrated improved endoscopic and overall symptom scores with minimal adverse effects.[44] A recent retrospective study by Jervis-Bardy et al.[45] evaluated the long-term effects of topical 0.05% mupirocin nasal irrigations and demonstrated a high-rate of re-culture positivity with *S. aureus* (73.7%), with a mean relapse time of 144 days. Sensitivities for the re-culture of *S. aureus* were provided and there was no increase in mupirocin resistance.[45] Although high-volume mupirocin saline irrigations have demonstrated promising results in *S. aureus*–positive refractory CRS, reinfection is common and further research is needed to further define the role of this topical therapy strategy in managing patients with CRS.

The current evidence on topical antibiotic therapy in the management of CRS is challenging to interpret because of significant study heterogeneity and limited level 1 quality research. Furthermore, there is minimal research evaluating the safety of topical antibiotic therapies, and the potential risks of bacterial resistance, local, and systemic adverse effects are concerning. The study by Desrosiers et al.[36] demonstrated that nebulized tobramycin increased nasal congestion. A retrospective review by Vaughan

TABLE 10. Summary of topical sinonasal antibiotic studies

Study	Year	Study design	LOE	No. of patterns included	Study groups	Treatment protocol	Primary clinical end-point	Conclusion Conclusion
Sykes et al.[35]	1986	RCT, placebo-controlled	2b	50	1) Neomycin, dexamethasone-tramazoline spray; 2) Dexamethasone-tramazoline spray; 3) Placebo	QID intranasal spray	1) Symptoms; 2) Bacterial culture; 3) Sinus X-ray; 4) Saccharin clearance; 5) Rhinomanometry; 6) Allergy testing	Significant improvement in groups 1 and 2 vs placebo. The addition of a topical antibiotic failed to offer any clinical benefit.
Desrosiers et al.[36]	2001	RCT, placebo-controlled	1b	20	1) Tobramycin-saline; 2) Saline alone (placebo)	TID intranasal large particle nebulizer; follow-up at 2 and 4 weeks	1) HRQoL (Juniper Rhinoconjunctivitis survey); 2) Endoscopy	Both groups received significant improvements. No difference with the addition of tobramycin.
Videler et al.[37]	2008	RCT, placebo-controlled	1b	14	1) Bacitracin/Colimycin; 2) Saline (placebo)	BID Rhinoflow nebulizer combined with oral levofloxacin	1) Symptoms; 2) QoL (SF-36); 3) Endoscopy	Both groups received significant improvements. No difference with the addition of Bacitracin/Colimycin.
Lim et al.[38]	2008	Systematic review	3a	14 studies evaluated	Included topical antibiotic and antifungal therapy	Variable depending on study	Variable depending on study	Level 1b studies demonstrate no benefit of topical antibiotic therapy using nebulized or spray delivery techniques. Lower-quality research suggests there may a positive effect. Little evidence on topical antibiotic therapy delivered using other techniques (ie, high-volume irrigations).

BID = twice daily; HRQoL = health-related quality of life; LOE = level of evidence; QID = 4 times daily; QoL = quality of life; RCT = randomized controlled trial; SF = Short Form; TID, 3 times daily.

et al.[46] reported a sore throat and cough in 9.5% and 7.5% of patients, respectively. Although rarely documented, there is a theoretic risk of oto- and nephrotoxicity with topical aminoglycoside therapy. Two small studies evaluating gentamycin nasal irrigations have demonstrated increased serum levels of gentamycin with no reported complications.[47,48] Clinical trials evaluating inhaled tobramycin have demonstrated increased tinnitus but failed to document a case of oto- or nephrotoxicity.[49] Although not documented in the sinonasal therapy literature, several studies evaluating inhaled nebulized antibiotics have demonstrated a risk of bronchoconstriction.[50,51] Last, the risk of bacterial resistance is a serious concern,[52] and appropriate use of both systemic and topical antibiotic therapies are important to consider.

Lower-quality studies suggest there may be a positive clinical effect, whereas 3 RCTs that used a nebulized or spray delivery technique demonstrated no difference in topical sinonasal antibiotic therapy compared to a placebo. Therefore, due to the lack of research supporting its efficacy, combined with limited safety data, we have produced a recommendation against using topical sinonasal antibiotic therapy, delivered using nebulized or spray techniques, for routine cases of CRS. However, there may be nonroutine cases of CRS when topical antibiotics, delivered using other delivery techniques (eg, irrigations), may be considered. If used for nonroutine cases of CRS, topical sinonasal antibiotic therapy should ideally be guided by cultures and sensitivities. Further randomized, double-blind, placebo-controlled trials are required to elucidate whether or not there is a clinical indication for topical sinonasal antibiotic therapy in the management of CRS.

Summary: Topical sinonasal antibiotic therapy

Aggregate quality of evidence. B (Level 1b: 2 studies; Level 2b: 1 study; Level 2c: 2 studies; Level 3a: 1 study; Level 4: 4 studies).

Benefit. Questionable improvement in patient-reported symptoms and endoscopic appearance in uncontrolled studies. Controlled clinical trials using low-volume delivery techniques failed to demonstrate a clinical benefit.

Harm. Local irrigation, cough, sore-throat. Nebulized tobramycin may increase nasal congestion. Potential risk of bronchoconstriction with some nebulized antibiotics. Potential risk of systemic adverse effects (oto- or nephrotoxicity) with topical aminoglycosides. Risk of bacterial resistance must be considered.

Cost. Moderate to high ($2.64 to $7.64); depends on agent used.

Benefits-harm assessment. Relative harm over benefit.

Value judgments. The authors of this review have used this therapy in select cases, but the most appropriate populations have yet to be defined. Clinical benefit only observed in lower-quality uncontrolled studies. Must balance the relatively unknown safety profile, monetary costs, and potential risk of bacterial resistance.

Recommendation level 1. Recommendation against—for nebulizer and spray delivery in routine cases of CRS.

Recommendation level 2. No recommendation—for other delivery methods (eg, irrigations).

Topical sinonasal antifungals

The role of fungus in the pathophysiology of CRS has long been debated.[53] In 1999, Ponikau et al.[54] hypothesized that fungal elements were responsible for inducing the mucosal inflammation characteristic of CRS and advocated for topical antifungal therapy. In 2002, a nonrandomized, noncontrolled pilot study demonstrated that topical amphotericin B resulted in both improved symptoms and endoscopic scores in patients with CRS.[55] This prompted a large number of RCTs evaluating topical antifungal therapy, most of which have failed to demonstrate a positive clinical impact. Although there are circumstances when fungus propagates sinonasal inflammation, such as "allergic" fungal rhinosinusitis, most experts believe that fungus is not a major contributor to CRS. Potential adverse effects of topical fungal therapy includes nasal burning, skin itching, acute exacerbation of CRS, and epistaxis.[56]

This review identified 5 RCTs[57–61] and 2 meta-analyses[56,62] evaluating the role of topical antifungals in patients with CRS (Table 11). There were 2 RCTs that evaluated topical antifungal therapy compared to placebo, but they were excluded from this article because they reported basic science, nonclinical end-points. Both of these basic science studies demonstrated no difference in the proinflammatory cytokine profile or culture rates.[63,64] Four of the 5 level 1b RCTs demonstrated no clinical difference between topical amphotericin B and placebo. Topical amphotericin B appears safe; however, Weschta et al.[61] reported an increase in adverse effects using topical amphotericin B. In 2005, Ponikau et al.[60] published the only study with positive clinical outcomes using topical amphotericin B in patients with CRS. The results were primarily limited to objective measures of endoscopy and computed tomography (CT) scan scores, whereas there was no difference in patient CRS HRQoL.

In 2011, 2 meta-analyses were published.[56,62] The study by Sacks et al.[56] quantitatively evaluated the evidence of topical antifungal therapy and demonstrated that there was no statistically significant difference between topical amphotericin B and placebo for the treatment of CRS. Furthermore, they demonstrated there was no increase in adverse effects with the use of topical amphotericin B. The authors concluded there is no evidence to support the use of topical

TABLE 11. Summary of topical sinonasal antifungal studies

Study	Year	Study design	LOE	No. of subjects	Study groups	Treatment protocol	Primary clinical end-point	Conclusion
Weschta et al.[61]	2004	RCT	1b	78	1) Amphotericin B; 2) Placebo	QID topical Amphotericin/placebo; follow-up at 8 weeks	1) Radiographic (CT); 2) Endoscopy; 3) HRQoL (RQLQ)	Worse symptoms scores with treatment.
Ponikau et al.[60]	2005	RCT	1b	30	1) Amphotericin B; 2) Placebo	BID topical Amphotericin/placebo; follow-up at 6 months	1) Radiographic (CT); 2) Endoscopy; 3) HRQoL (SNOT-20); 4) Blood eosinophilia, inflammatory mediator levels; 5) Intranasal alternaria protein	Significant improvement in endoscopy and CT findings. No significant differences in serum eosinophilia or HRQoL.
Ebbens et al.[57]	2006	RCT	1b	116	1) Amphotericin B; 2) Placebo	BID topical Amphotericin/placebo; follow-up at 2, 6, and 13 weeks	1) Symptoms; 2) Endoscopy; 3) QoL (SF-36); 4) HRQoL (RSOM-31); 5) Peak nasal inspiratory flow	Improvement in both groups but no difference between groups. Indirect evidence that nasal irrigation alone improves symptoms.
Weschta et al.[64]	2006	RCT	1b	76	1) Amphotericin B; 2) Placebo	QD topical Amphotericin/placebo; follow-up at 8 weeks	1) Fungal culture/PCR; 2) Eosinophilic cationic protein and Tryptase levels in nasal lavage	No difference between groups.
Liang et al.[59]	2008	RCT	1b	64	1) Amphotericin B; 2) Placebo	QD topical amphotericin B/placebo; follow-up at 2and 4 weeks	1) Endoscopy; 2) HRQoL (RSOM-31); 3) Bacterial/fungal cultures	No significant difference between groups.
Ebbens et al.[63]	2009	RCT	1b	39	1) Amphotericin B; 2) Placebo	BID topical Amphotericin/placebo; follow-up at 2, 6, and 13 weeks	1) Levels of pro inflammatory cytokines, chemokines, and growth factors in nasal lavage samples	No significant difference between groups.
Gerlinger et al.[58]	2009	RCT	1b	33	1) Amphotericin B; 2) Placebo	Follow-up at 1 year after ESS	1) Radiographic (CT); 2) SNAQ-11 (assess change in symptoms); 3) Endoscopic	No significant difference between groups.
Isaacs et al.[62]	2011	Meta-analysis	1a	5 level 1b studies	1) Amphotericin B; 2) Placebo	Variable depending on study	1) Symptom; 2) Endoscopy; 3) Radiologic (CT)	No difference between topical sinonasal amphotericin B and all 3 outcomes: symptom, endoscopy, and CT scores.
Sacks et al.[56]	2011	Meta-analysis	1a	5 level 1b studies	1) Amphotericin B; 2) Placebo	Variable depending on study	1) Subjective outcomes; 2) Objective outcomes; 3) Adverse effects	No evidence for topical antifungal in routine management of CRS.

BID = twice daily; CRS = chronic rhinosinusitis; CT = computed tomography; HRQoL = health-related quality of life; LOE = level of evidence; PCR = polymerase chain reaction; QD = once daily; QID = 4 times daily; QoL = quality of life; RCT = randomized controlled trial; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; RSOM = Rhinosinusitis Outcome Measure; SF = Short Form; SNAQ = Sinonasal Assessment Questionnaire; SNOT = Sinonasal Outcome Test.

International Forum of Allergy & Rhinology

antifungal therapy in the management of CRS. The study by Isaacs et al.[62] quantitatively evaluated 3 clinical end-points and demonstrated that amphotericin B fails to improve patient symptom scores, CT scores, and endoscopy grading.

Summary: Topical sinonasal antifungal therapy

Aggregate evidence. A (negative) (Level 1a: 2 studies; Level 1b: 5 studies).

Benefit. One study out of 5 demonstrated an improved CT score and endoscopic appearance.

Harm. Nasal burning, acute exacerbation of CRS, epistaxis, rash, and asthma attack.

Cost. No market price available.

Benefits-harm assessment. Preponderance of harm over benefit.

Value judgments. None.

Recommendation level. Strong recommendation against.

Topical alternatives

Medically and surgically refractory CRS is a very challenging clinical scenario that has resulted in the development of several nontraditional topical therapies. This section will briefly discuss 3 promising topical therapy options that have been recently reported. However, given the relative lack of evidence, we are unable to generate aggregate evidence tables and recommendations for these therapies at this time.

The surfactant component of baby shampoo saline irrigations is thought to be an effective treatment against biofilm associated with CRS. In 2008, Chiu et al.[65] used a 1% baby shampoo irrigation twice-daily protocol in medically refractory CRS and demonstrated a 47% overall symptom improvement, and a 60% improvement in postnasal drainage. There was no effect on preformed pseudomonas biofilm but shampoo functioned to inhibit biofilm formation.[65] A recent study by Isaacs et al.[66] evaluated mucociliary clearance time using a saccharin test following a 50-mL 1% baby shampoo saline irrigation and demonstrated increased mucociliary time in the baby shampoo group compared to saline alone (15.45 minutes vs 12.09 minutes, respectively; $p = 0.031$). Sinusurf® is a recently introduced product that is composed of the isolated surfactant component of baby shampoo. Evidence on this topical therapy is limited and, due to some adverse effects, it has been recently recalled (August 2011) for further investigation. Side-effects included nasal burning, foul taste, epistaxis, headache, and smell disturbance.[67]

Manuka honey, and the active component, methylglyoxal (MGO), have been demonstrated to possess anti-*Staphylococcus* and anti-*Pseudomonas* biofilm properties in vitro.[68,69] A recent study by Kilty et al.[70] evaluated the safety effects of manuka honey on rabbit respiratory mucosa and demonstrated no evidence of epithelial injury or morphological changes. A recent in vitro study by Jervis-Bardy et al.[68] evaluated the biofilm-cidal activity of manuka honey and MGO-only solutions. They demonstrated that biofilm-cidal activity was obtained with manuka honey solutions which contain a MGO concentration of >0.53 mg/mL and MGO-only solutions of >1.05 mg/mL, indicating that MGO is only partially responsible for the antibiofilm effects.[68] An in vivo study by Thamboo et al.[71] evaluated manuka honey irrigation in patients with allergic fungal rhinosinusitis and failed to demonstrate an overall endoscopic improvement. However, there was a small subset of patients that received a significant endoscopic improvement, and further research is needed to elucidate the factors to predict a positive clinical impact. More in vivo research is required to determine the effects of manuka honey and MGO in patients with CRS.

Xylitol is a naturally occurring organic sugar alcohol compound that has been demonstrated to possess antibacterial and antibiofilm properties.[72,73] A recent pilot study by Weissman et al.[74] performed a randomized, double-blind controlled trial to evaluate whether xylitol saline irrigations result in symptomatic improvement in patients with CRS. The results demonstrated that there was a significant improvement in HRQoL scores (2.43 point reduction in SNOT-22 score) during the 10-day xylitol irrigation period compared to the saline irrigation period. There was no change in visual analogue scale (VAS) symptom scores and there were no differences in adverse effects. Three of 20 patients reported a dislike for the sweet taste associated with the xylitol irrigation. This is the first in vivo study evaluating topical xylitol for the management of CRS, and future research is needed to further evaluate this potential therapy.

Summary: Topical sinonasal alternative therapy

Aggregate evidence. N/A—variety of agents evaluated.

Benefit. Reduced postnasal drip. Improved HRQoL and endoscopic appearance.

Harm. Nasal burning, impaired ciliary function, unpleasant tastes.

Cost. No market prices available.

Benefits-harm assessment. Unknown.

TABLE 12. Summary of topical sinonasal therapy for the management of CRS

Topical therapy strategy	Grade of evidence	Balance of benefit to harm	Recommendation level	Topical therapy protocol
Saline irrigation	B	Benefit	Recommendation	Use high-volume sinonasal saline irrigations as an adjunct to other topical therapies in the management of CRS
Standard topical steroid	A	Benefit	Strong recommendation	Use standard metered-dose topical nasal steroid spray in the management of CRS
Nonstandard topical steroid	C	Equal	Option	Off-label sinonasal options include: 1) Budesonide nasal irrigations (0.5 mg/2 mL or 1 mg/2 mL in 240 mL saline irrigation); 2) Intranasal dexamethasone ophthalmic drops (0.1%); 3) Intranasal prednisolone ophthalmic drops (1%); 4) Intranasal ciprofloxacin/dexamethasone otic drops (0.3/0.1%)
Topical antibiotic	B	Harm	1) Recommendation against—for nebulizer and spray delivery in routine cases of CRS; 2) No recommendation—for other delivery methods	Highly variable
Topical antifungal	A	Harm	Strong recommendation against	N/A
Alternative therapies	N/A	N/A	No recommendation	N/A

CRS = chronic rhinosinusitis; N/A = not available.

Value judgments. Need more research to provide evidence-based recommendations.

Recommendation level. No recommendation.

Overall summary

Based on the best available evidence, an evidenced-based topical therapy protocol in the management of CRS would include sinonasal saline irrigation and standard topical nasal steroid therapy. There is an option for the use of nonstandard (off-label) high-concentration topical sinonasal steroid therapy. In such instances, the option level assignment for off-label topical sinonasal steroid intervention would require shared decision-making and discussion with the patient prior to prescribing. The evidence suggests that topical sinonasal antibiotic therapy delivered using either a nebulized or spray technique fails to provide clinical benefit, and when combined with a preponderance for harm, we provided a recommendation against its use in routine cases of CRS. There is not enough evidence to evaluate topical antibiotic therapy using other delivery techniques and therefore we provided no recommendation for this therapeutic intervention. There is strong evidence to recommend against the use of topical antifungal therapy in the management of CRS (Table 12).

There are several alternative topical therapies that have been described and evaluated in the management of CRS. The use of topical surfactant (baby shampoo), manuka honey (or MGO), or xylitol irrigations requires further research before any recommendations can be produced.

Conclusion

This review evaluated the literature on 5 different topical sinonasal therapy strategies for the management of CRS using a specific protocol for the development of an evidence-based review with recommendations. An evidence-based topical therapy protocol in the management of CRS would include the use of daily high-volume sinonasal saline irrigation in combination with standard metered-dose topical nasal steroid spray. Due to a relative balance between possible therapeutic advantages and potential adverse effects, the use of a nonstandard (off-label) topical sinonasal steroid solution is an option in the management of CRS. Future research will need to evaluate promising alternative topical sinonasal therapies such as baby shampoo/surfactant,

manuka honey, and xylitol irrigations. These evidence-based recommendations should not necessarily be applied to all CRS patients, and clinical judgment, in addition to available evidence, is critical to determining the most appropriate care, particularly given the heterogeneity of CRS. Potential future randomized trials include:

1. Evaluation of different delivery techniques for standard topical steroid therapy.
2. Evaluation of different off-label steroid therapy in patients with CRS. Defining optimal dose, frequency, and duration.
3. Evaluation of different topical antibiotic delivery methods and agents in CRS.
4. Evaluation of the safety profile for topical sinonasal antibiotic therapy.
5. Evaluation of topical alternative therapies in different CRS cohorts.

References

1. Soler ZM, Wittenberg E, Schlosser RJ, Mace JC, Smith TL. Health state utility values in patients undergoing endoscopic sinus surgery. *Laryngoscope* 2011;121:2672–2678.
2. Bhattacharyya N, Orlandi RR, Grebner J, Martinson M. Cost burden of chronic rhinosinusitis: a claims–based study. *Otolaryngol Head Neck Surg* 2011;144:440–445.
3. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. *Otolaryngol Head Neck Surg* 2008;139:137–142.
4. Rudmik L, Smith TL. Development of an evidence-based review with recommendations using an online iterative process. *Int Forum Allergy Rhinol* 2011;1:431–437.
5. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* 2007;137:S1–S31.
6. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 2003;129:S1–S32.
7. Oxford Centre for Evidence-based Medicine (CEBM). Levels of Evidence. 2009. http://www.cebm.net/index.aspx?o = 1025. Accessed September 2, 2012.
8. American Academy of Pediatrics Steering Committee on Quality Improvement and Management (AAP SCQIM): classifying recommendations for clinical practice guidelines. *Pediatrics* 2004;114:874–877.
9. 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. *Ann Fam Med* 2006;4:295–301.
10. 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. *J Fam Pract* 2002;51:1049–1055.
11. Bachmann G, Hommel G, Michel O. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. *Eur Arch Otorhinolaryngol* 2000;257:537–541.
12. Heatley DG, McConnell KE, Kille TL, Leverson GE. Nasal irrigation for the alleviation of sinonasal symptoms. *Otolaryngol Head Neck Surg* 2001;125:44–48.
13. Pinto JM, Elwany S, Baroody FM, Naclerio RM. Effects of saline sprays on symptoms after endoscopic sinus surgery. *Am J Rhinol* 2006;20:191–196.
14. Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. *Otolaryngol Head Neck Surg* 2007;137:815–821.
15. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. *Arch Otolaryngol Head Neck Surg* 2007;133:1115–1120.
16. Freeman SR, Sivayoham ES, Jepson K, de Carpentier J. A preliminary randomised controlled trial evaluating the efficacy of saline douching following endoscopic sinus surgery. *Clin Otolaryngol* 2008;33:462–465.
17. Liang KL, Su MC, Tseng HC, Jiang RS. Impact of pulsatile nasal irrigation on the prognosis of functional endoscopic sinus surgery. *J Otolaryngol Head Neck Surg* 2008;37:148–153.
18. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2007:CD006394.
19. Nasonex. Product Information. 2010. http://www.spfiles.com/pinasonex.pdf. Accessed September 2, 2012.
20. Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008;139:340–347.
21. Kalish LH, Arendts G, Sacks R, Craig JC. Topical steroids in chronic rhinosinusitis without polyps: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2009;141:674–683.
22. Rudmik L, Schlosser RJ, Smith TL, Soler ZM. Impact of topical nasal steroid therapy on symptoms of nasal polyposis: a meta-analysis. *Laryngoscope* 2012;122:1431–1437.
23. Snidvongs K, Kalish L, Sacks R, Craig JC, Harvey RJ. Topical steroid for chronic rhinosinusitis without polyps. *Cochrane Database Syst Rev* 2011:CD009274.
24. Snidvongs K, Kalish L, Sacks R, R. S, D. C, Harvey RJ. Topical steroids for nasal polyps. *Cochrane Database Syst Rev* 2012.
25. DelGaudio JM, Wise SK. Topical steroid drops for the treatment of sinus ostia stenosis in the postoperative period. *Am J Rhinol* 2006;20:563–567.
26. Rotenberg BW, Zhang I, Arra I, Payton KB. Postoperative care for Samter's triad patients undergoing endoscopic sinus surgery: a double-blinded, randomized controlled trial. *Laryngoscope* 2011;121:2702–2705.
27. Steinke JW, Payne SC, Tessier ME, Borish LO, Han JK, Borish LC. Pilot study of budesonide inhalant suspension irrigations for chronic eosinophilic sinusitis. *J Allergy Clin Immunol* 2009;124:1352–1354.e7.
28. Snidvongs K, Pratt E, Chin D, Sacks R, Earls P, Harvey RJ. Corticosteroid nasal irrigations after endoscopic sinus surgery in the management of chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2012.
29. Sachanandani NS, Piccirillo JF, Kramper MA, Thawley SE, Vlahiotis A. The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 2009;135:303–307.
30. Kanowitz SJ, Batra PS, Citardi MJ. Topical budesonide via mucosal atomization device in refractory postoperative chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008;139:131–136.
31. Bhalla RK, Payton K, Wright ED. Safety of budesonide in saline sinonasal irrigations in the management of chronic rhinosinusitis with polyposis: lack of significant adrenal suppression. *J Otolaryngol Head Neck Surg* 2008;37:821–825.
32. Welch KC, Thaler ER, Doghramji LL, Palmer JN, Chiu AG. The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. *Am J Rhinol Allergy* 2010;24:26–28.
33. Cervin A, Wallwork B. Macrolide therapy of chronic rhinosinusitis. *Rhinology* 2007;45:259–267.
34. Soler ZM, Smith TL. What is the role of long-term macrolide therapy in the treatment of recalcitrant chronic rhinosinusitis? *Laryngoscope* 2009;119:2083–2084.
35. Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study. *Lancet* 1986;2:359–360.
36. Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. *Otolaryngol Head Neck Surg* 2001;125:265–269.
37. Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with *Staphylococcus aureus*? A double-blind, randomized, placebo-controlled, cross-over pilot study. *Rhinology* 2008;46:92–98.
38. Lim M, Citardi MJ, Leong JL. Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. *Am J Rhinol* 2008;22:381–389.
39. Kamijyo A, Matsuzaki Z, Kikushima K, et al. Fosfomycin nebulizer therapy to chronic sinusitis. *Auris Nasus Larynx* 2001;28:227–232.
40. Kobayashi T, Baba S. Topical use of antibiotics for paranasal sinusitis. *Rhinol Suppl* 1992;14:77–81.
41. Leonard DW, Bolger WE. Topical antibiotic therapy for recalcitrant sinusitis. *Laryngoscope* 1999;109:668–670.
42. Solares CA, Batra PS, Hall GS, Citardi MJ. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant *Staphylococcus aureus* with mupirocin irrigations. *Am J Otolaryngol* 2006;27:161–165.
43. Le T, Psaltis A, Tan LW, Wormald PJ. The efficacy of topical antibiofilm agents in a sheep model of rhinosinusitis. *Am J Rhinol* 2008;22:560–567.
44. Uren B, Psaltis A, Wormald PJ. Nasal lavage with mupirocin for the treatment of surgically recalcitrant chronic rhinosinusitis. *Laryngoscope* 2008;118:1677–1680.
45. Jervis-Bardy J, Wormald PJ. Microbiological outcomes following mupirocin nasal washes for symptomatic, *Staphylococcus aureus*–positive chronic rhinosinusitis following endoscopic sinus surgery. *Int Forum Allergy Rhinol* 2012;2:111–115.
46. Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. *Otolaryngol Head Neck Surg* 2002;127:558–568.
47. Whatley WS, Chandra RK, MacDonald CB. Systemic absorption of gentamicin nasal irrigations. *Am J Rhinol* 2006;20:251–254.
48. Wong KK, Marglani O, Westerberg BD, Javer AR. Systemic absorption of topical gentamicin sinus irrigation. *J Otolaryngol Head Neck Surgery* 2008;37:395–398.
49. Cheer SM, Waugh J, Noble S. Inhaled tobramycin (TOBI): a review of its use in the management of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. *Drugs* 2003;63:2501–2520.
50. Conway SP. Nebulized antibiotic therapy: the evidence. *Chron Respir Dis* 2005;2:35–41.
51. Alothman GA, Ho B, Alsaadi MM, et al. Bronchial constriction and inhaled colistin in cystic fibrosis. *Chest* 2005;127:522–529.
52. Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century—a clinical super-challenge. *N Engl J Med* 2009;360:439–443.
53. Ebbens FA, Georgalas C, Rinia AB, van Drunen CM, Lund VJ, Fokkens WJ. The fungal debate: where do we stand today? *Rhinology* 2007;45:178–189.
54. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc* 1999;74:877–884.
55. Ponikau JU, Sherris DA, Kita H, Kern EB. Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2002;110:862–866.
56. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2011:CD008263.
57. Ebbens FA, Scadding GK, Badia L, et al. Amphotericin B nasal lavages: not a solution for patients

with chronic rhinosinusitis. *J Allergy Clin Immunol* 2006;118:1149–1156.

58. Gerlinger I, Fittler A, Fonai F, Patzko A, Mayer A, Botz L. Postoperative application of amphotericin B nasal spray in chronic rhinosinusitis with nasal polyposis, with a review of the antifungal therapy. *Eur Arch Otorhinolaryngol* 2009;266:847–855.
59. Liang KL, Su MC, Shiao JY, et al. Amphotericin B irrigation for the treatment of chronic rhinosinusitis without nasal polyps: a randomized, placebo-controlled, double-blind study. *Am J Rhinol* 2008;22:52–58.
60. Ponikau JU, Sherris DA, Weaver A, Kita H. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. *J allergy Clin Immunol* 2005;115:125–131.
61. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. *J allergy Clin Immunol* 2004;113:1122–1128.
62. Isaacs S, Fakhri S, Luong A, Citardi MJ. A meta-analysis of topical amphotericin B for the treatment of chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2011;1:250–254.
63. Ebbens FA, Georgalas C, Luiten S, et al. The effect of topical amphotericin B on inflammatory markers in patients with chronic rhinosinusitis: a multicenter randomized controlled study. *Laryngoscope* 2009;119:401–408.
64. Weschta M, Rimek D, Formanek M, Podbielski A, Riechelmann H. Effect of nasal antifungal therapy on nasal cell activation markers in chronic rhinosinusitis. *Arch Otolaryngol Head Neck Surg* 2006;132:743–747.
65. Chiu AG, Palmer JN, Woodworth BA, et al. Baby shampoo nasal irrigations for the symptomatic postfunctional endoscopic sinus surgery patient. *Am J Rhinol* 2008;22:34–37.
66. Isaacs S, Fakhri S, Luong A, Whited C, Citardi MJ. The effect of dilute baby shampoo on nasal mucociliary clearance in healthy subjects. *Am J Rhinol Allergy* 2011;25:e27–e29.
67. NeilMed Pharmaceuticals. SinuSurf® Information. August 2011. http://www.neilmed.com/usa/ssinfo.php. Accessed September 2, 2012.
68. Jervis-Bardy J, Foreman A, Bray S, Tan L, Wormald PJ. Methylglyoxal-infused honey mimics the anti-*Staphylococcus aureus* biofilm activity of manuka honey: potential implication in chronic rhinosinusitis. *Laryngoscope* 2011;121:1104–1107.
69. Alandejani T, Marsan J, Ferris W, Slinger R, Chan F. Effectiveness of honey on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms. *Otolaryngol Head Neck Surg* 2009;141:114–118.
70. Kilty SJ, AlMutairi D, Duval M, Groleau MA, De Nanassy J, Gomes MM. Manuka honey: histological effect on respiratory mucosa. *Am J Rhinol Allergy* 2010;24:e63–e6.
71. Thamboo A, Thamboo A, Philpott C, Javer A, Clark A. Single-blind study of manuka honey in allergic fungal rhinosinusitis. *Otolaryngol Head Neck Surg* 2011;40:238–243.
72. Brown CL, Graham SM, Cable BB, Ozer EA, Taft PJ, Zabner J. Xylitol enhances bacterial killing in the rabbit maxillary sinus. *Laryngoscope* 2004;114:2021–2024.
73. Kurola P, Tapiainen T, Sevander J, et al. Effect of xylitol and other carbon sources on *Streptococcus pneumoniae* biofilm formation and gene expression in vitro. *APMIS* 2011;119:135–142.
74. Weissman JD, Fernandez F, Hwang PH. Xylitol nasal irrigation in the management of chronic rhinosinusitis: a pilot study. *Laryngoscope* 2011;121:2468–2472.