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Topical Drug Delivery for Chronic Rhinosinusitis

Jonathan Liang, MD and **Andrew P. Lane, MD**
Department of Otolaryngology Head and Neck Surgery, Johns Hopkins University School of Medicine

Abstract

Chronic rhinosinusitis is a multifactorial disorder that may be heterogeneous in presentation and clinical course. While the introduction of endoscopic sinus surgery revolutionized surgical management and has led to significantly improved patient outcomes, medical therapy remains the foundation of long-term care of chronic rhinosinusitis, particularly in surgically recalcitrant cases. A variety of devices and pharmaceutical agents have been developed to apply topical medical therapy to the sinuses, taking advantage of the access provided by endoscopic surgery. The goal of topical therapy is to address the inflammation, infection, and mucociliary dysfunction that underlies the disease. Major factors that impact success include the patient's sinus anatomy and the dynamics of the delivery device. Despite a growing number of topical treatment options, the evidence-based literature to support their use is limited. In this article, we comprehensively review current delivery methods and the available topical agents. We also discuss biotechnological advances that promise enhanced delivery in the future, and evolving pharmacotherapeutical compounds that may be added to rhinologist's armamentarium. A complete understand of topical drug delivery is increasingly essential to the management of chronic rhinosinusitis when traditional forms of medical therapy and surgery have failed.

Keywords

topical; drug delivery; chronic rhinosinusitis; saline; antimicrobials; corticosteroids

Introduction

Since its introduction over three decades ago[1], endoscopic sinus surgery (ESS) has become the standard of care for the treatment of medically recalcitrant chronic rhinosinusitis (CRS). The primary goal of functional endoscopic sinus surgery is to improve patient symptoms by restoring ostial patency and mucociliary function. As experience with endoscopic sinus surgery has grown, it has become apparent that these aims are achieved most successfully when inflammatory sinus disease stems principally from anatomic obstruction. In some forms of CRS, however, there appears to be an intrinsic mucosal inflammatory component that is not directly amenable to surgical correction. In these cases, the goals of the endoscopic procedure shift from reversing the disease process to providing *access* for long-term sinonasal endoscopic surveillance and the application of topical therapies. Locally-delivered pharmacotherapy has increasingly been viewed as a new frontier in CRS management, and the armamentarium of topical options has greatly expanded over the past

Corresponding author: Andrew P. Lane, MD, Department of Otolaryngology Head and Neck Surgery, Johns Hopkins University School of Medicine, 601 N. Caroline St., 6th Floor, Baltimore, MD 21287, Phone: 410-955-7808, Fax: 410-614-8610, alane3@jhmi.edu.

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decade. To understand the current and future status of topical therapies for CRS, knowledge of the methods of delivery as well as the available drugs and compounds is needed. The scientific evidence supporting topical therapy for CRS remains most robust for long-utilized agents such as saline and intranasal corticosteroid sprays. While newer topical preparations such as antimicrobials, surfactant agents, and organic natural products are continuing to advance the ability of physicians to manage inflammatory sinus disease, the choice of specific agents and the optimal mechanisms of delivery remain subjects of active investigation and debate.

Three mechanisms have been proposed to centrally contribute to CRS pathophysiology: mucosal inflammation, local infection, and mucociliary dysfunction[2–3]. Topical medical therapy has been designed to target each of these, and its success relies upon both mechanical irrigation and pharmaceutical delivery[4–5]. Irrigation helps to removal pollutants, antigens, inflammatory byproducts, mucus, and bacteria from the sinonasal tract. Factors that optimize the mechanical action of topical therapy often do so at the expense of optimal drug delivery, for which prolonged mucosal contact time and minimal depletion are desirable[5]. These competing goals present challenges in developing medications and delivery systems for the treatment of CRS.

Methods of Delivery

Sinonasal drug delivery fluid dynamics is a rapidly growing area of intense research investigation. This high level of interest is directly tied to a number of commercial products, each with variable published experimental support. Studies on delivery methods have focused on the state of the paranasal sinuses (non-operated vs. post-surgical) and the device dynamics (device, techniques, volume, position).

Sinus surgery is a pre-requisite for effective sinus topical drug delivery

It is well established that the delivery of topical solution to the non-operated sinuses is very limited[6]. Pressurized nasal spray provide only nasal cavity penetration at best, and squeeze bottle and Neti pot irrigation only provided some maxillary sinus and ethmoid sinus penetration[6]. The frontal and sphenoid sinuses are essentially not accessible prior to surgery[6]. Olson evaluated three methods of nasal irrigation in healthy non-operated individuals found distribution in the nasal cavity, but poor distribution in the sinuses with all techniques[7]. With CRS, mucosal inflammation and edema further limit the penetration of nasal irrigation or sprays[8]. Grobler *et al.* showed that an ostial size of greater than 3.95 mm is required to see penetration into the maxillary sinus[9].

Endoscopic sinus surgery allows for more effective delivery of topical drugs, although the degree to which access is increased depends on the extent and technique of surgery. With the advent of balloon dilation technology, an even wider variability in the size of “post-surgical” sinus openings exists. This heterogeneity creates a confounding variable in determining the effectiveness of topical drug delivery in post-surgical sinus cavities. In Harvey’s cadaveric study, delivery to the sinuses improved after sinus surgery regardless of the delivery device[6]. Studies have shown that irrigation with douching or bulb irrigation is more effective than sprays, nebulizers, or atomizers in reaching post-operative sinus cavities[10–11].

Devices to deliver saline

There are a number of devices on the market for topical saline delivery into the nose and paranasal sinuses. They vary mainly in the volume and pressure of delivery (Table 1). Regardless of device or technique, penetration into the sinuses is very limited in non-operated sinuses[6, 8–9]. Two common high-volume techniques for delivery of nasal saline are

the squeeze bottle (high pressure) and the Neti pot (low pressure). Large volume systems have been shown to have the best efficacy in post-ESS cavities, with large volume high pressure devices being superior[6, 9–12]. Low volume devices, such as pump spray (high pressure) or nebulizer (low pressure), poorly penetrate the sinuses even after ESS[6, 12]. Less than 50% of most low volume devices reach the middle meatus[13]. Low volume systems should be considered a nasal cavity treatment because both pre- and post-surgical penetration into the sinuses is extremely poor.

Drug delivery devices

Nasal pump sprays are a popular option for topical drug delivery because of their ease of use, and many different formulations are available in this format. The main factors associated with particle penetration include the size of the sinus ostia, the size of the particle, and the flow rate of the aerosol[14–15]. Particles >10 μm in size usually do not make it past the nasal cavity, and particles <5 μm are needed to enter into the lungs. Hyo *et al.* theorized that ideal particle size for maxillary sinus penetration is between 3 to 10 μm, and further work by Saijo *et al.* demonstrated that smaller particle size (5.63 μm vs. 16.37 μm), 45 insertion angle (vs. 30 insertional angle), and higher flow rate improved maxillary sinus penetration[14, 16].

Typical nasal pump sprays generate droplets of 50 to 100 μm in diameter size, and deliver 70 to 150 μL of drug per puff, at standard velocities of 7.5 to 20 L/min[5]. A large fraction of the spray is deposited in the anterior nasal cavity without any significant penetration into the paranasal sinuses[17–18]. Furthermore, half of the aerosol is cleared after approximately 15 minutes, with minimal activity remaining after 6 hours[17–18]. A breath-actuated bidirectional delivery device (OptiMist™; OptiNose AS, Oslo, Norway) has been developed to address the limitations of nasal pump spray. This device, generating drops of 43 μm diameter, demonstrates larger cumulative deposition in the region of the middle meatus and less anterior segment deposition compared to a conventional nasal pump spray[19].

Nebulizers deliver medication in mist form, and are commonly used to delivery drugs to the lower airway. A variety of nebulizers have been developed for targeted sinonasal drug delivery (Table 2). SinuNeb™ (PARI Respiratory Equipment, Inc, Midlothian, VA) is a passive-diffusion system; ViaNase™ (Kurve Technology Inc, Lynnwood, WA) is a vortex-propelled system[12]. PARI Sinus™ Pulsating Aerosol System (PARI GmbH, Starnberg, Germany) is a pulsating nebulizer that has refined particle size distribution and flow rate[20]. Studies on the pulsating aerosol system demonstrated improved posterior nasal cavity deposition with access to the ostiomeatal complex and slower clearance times compared with nasal pump sprays[17–18, 20]. Although nebulizers represent a more technologically evolved form of a traditional spray pump, the literature to support the efficacy of drug delivery with nebulizers is still poor[7, 10, 12, 21].

Patient positioning for drug delivery

There is no consensus on the most effective position for delivering topical drugs into the nose and paranasal sinuses. Many commercial products recommend a head-down, over-the-sink, or nose-toground position for nasal irrigation. This makes the residual runoff easy to collect and is practical for patients. The delivery of nasal drops relative to head position has been studied[13, 22]. One study found that the “Mygind” and “Ragan” (left lateral and supine) positions were more effective than the “Mecca” and “Head Back” positions for delivery into the middle meatus[22]. However, this has not been supported in other studies[13, 23–26]. Head-down or “vertex-to-floor” position has been suggested to lead to better frontal distribution post-ESS[27]. Positioning is more relevant for low-pressure delivery systems. For example, when using the neti pot, the “Mygind” head position allows for the gravity-dependent

drainage into the contralateral nasal wall and sinuses. Positioning with high-pressure delivery systems may have less clinical importance[5].

Drugs and Compounds

Saline

Saline irrigations and sprays are the most commonly used intervention for rhinitis and rhinosinusitis. Nasal saline has its roots in homeopathic medicine. Nasal washing is an ancient Ayurvedic technique known as “Jala neti”, which means nasal cleansing in Sanskirt. Today, it is often used as an adjunctive treatment for treatment of chronic rhinosinusitis. Its use has been advocated both before and following sinus surgery, and in the latter case to thoroughly cleanse the sinonasal passages and promote mucosal healing. Much of the support for this intervention has been anecdotal, however recent literature provided evidence to support the use of nasal saline for symptom improvement[28].

The physiological basis for the benefit of saline is unclear. The mechanical clearance of mucus by saline is thought to be the most important factor. Both isotonic and hypertonic saline appear to have a positive effect on mucociliary transport time[29–30]. This is thought to be due to improved rheologic properties of the sol layer rather than improved ciliary beat frequency[31–32], although the data regarding ciliary beat frequency has been conflicting[32–33]. Other theories on the beneficial effects of saline include its nasal mucosal protective effect and its ability to remove antigens, inflammatory mediators, and biofilm.

A Cochrane review reported that saline improves symptoms and disease specific quality of life scores when compared to no treatment, either a single modality or as an adjunctive treatment[28]. Although there is evidence that hypertonic solutions improve mucociliary clearance[30, 34], no difference was found in symptoms scores when comparing isotonic (0.9%) to hypertonic saline[28]. Hypertonic preparations have been shown to elicit some pain and discomfort at concentration above 2.7%[35]. At concentrations approaching 5.4%, patients experience significant nasal obstruction due to vasodilation and there is reduced airspace as determined by acoustic rhinometry[35].

The common delivery methods of topical saline include squeeze bottle, atomized spray, and Neti pot. There have been few studies comparing the efficiency of saline on symptom scores by means of delivery mechanism. Pynnonen *et al.* showed greater efficacy of saline irrigation versus saline spray for providing short term relief of chronic nasal symptoms[36]. This study focused on a community population of patients with sinonasal complaints and excluded patients with recent sinus surgery. The efficacy of saline in non-operated verses post-surgical must be inferred from the aforementioned anatomic studies[28].

Saline is the cornerstone of treatment in the rhinologist’s armamentarium of topical therapy for CRS, in part because it is very low risk with minimal adverse effects. The Cochrane study showed no serious adverse event in over 1650 patients in published trials[28]. Most patients tolerate nasal saline irrigation well, and even recommend this to family and friends with sinus problems[37]. A small subset of patients will not tolerate nasal saline irrigation due to discomfort or inconvenience. The most common minor complaints include nasal burning, irritation, and nausea[28]. Delivery systems have developed around topical saline to improve distribution and patient compliance. Since there are currently no approved drugs for the treatment of CRS, saline delivery systems are often employed for off-label use of drugs as topical agents.

Corticosteroids

Corticosteroids are potent medications that broadly target pro-inflammatory pathways. While CRS is a heterogeneous disorder with a multifactorial etiology, mucosal inflammation is a cardinal feature of the disease that contributes to the symptoms and histopathology. Both systemic and topical corticosteroids are used to treat chronic rhinosinusitis with and without nasal polyposis (CRSsNP and CRSwNP, respectively). Topical corticosteroids are favored over systemic corticosteroids because of the decreased potential for significant side effects, especially with prolonged use.

Topical nasal steroids are effective for the treatment of CRSwNP, and are often considered a first-line treatment option[38–39]. Currently, only one intranasal steroid, mometasone furoate is FDA-approved for the treatment of nasal polyps in CRS. However, various non-approved topical steroids are commonly used in practice today. There is strong evidence for the treatment of CRSwNP with intranasal steroids in terms of reducing polyp size on endoscopic examination[39]. Topical mometasone, fluticasone, and budesonside have the best evidence for use, especially in the post-ESS state[39]. On the other hand, the evidence for intranasal steroids for CRSsNP is not well-established. A Cochrane review on CRSsNP found that intranasal steroids improved symptoms overall, but the pooled studies were diverse in outcome measures, delivery methods, and surgical status[40]. Similarly, a meta-analysis found insufficient evidence that intranasal steroids demonstrated a clear benefit in CRSsNP[41].

An emerging trend for the treatment of refractory CRSwNP is the use of “off label” otic, ophthalmic, or respiratory formulations of corticosteroids as topical agents delivered to the nose[42–44]. Budesonide irrigations have gained significant recent interest in the U.S. It is often prescribed as a 0.5 mg in 2 mL respules diluted in 240 mL squeeze bottle irrigation to be used twice daily. Initial studies have shown no evidence of adrenal suppression[44–46]. In the United Kingdom and some areas of Europe, solutions of either betamethasone or fluticasone propionate are commercially available as nasal drops and used to treat CRSwNP[47].

Nasal pump sprays, the most common delivery method of intranasal corticosteroids, have almost no sinus penetration in non-operated patients[6, 21]. Snidvongs *et al.* found no difference in terms of symptom scores or response to treatment between non-operated and post-operative patients[40]. Other methods for delivery of corticosteroids into the sinonasal cavity include aerosol, irrigation, and nasal drops. Some studies have reported delivery via direct cannulation via an intranasal tube[48] or intrasinus tube[49–50]. The Cochrane review showed no difference in outcomes based on delivery method[40]. Topical corticosteroids can cause minor side effects of headaches, epistaxis, dryness or burning; significant adverse events are extremely rare[51].

Antibiotics

Oral antibiotics are effective in the treatment of chronic sinusitis and its acute exacerbations[52–54]. Topical antibiotics have thus emerged as adjunctive treatment for CRS because they offer the potential for high local concentration at the desired target site with minimization of systemic side effects. The literature supports both nebulized- and irrigation-type preparations of topical antibiotics. A systematic review found some evidence for irrigated or nebulized antimicrobials, but no evidence for delivery by nasal sprays[55]. Irrigation with topical antibiotics has been shown to be effective in CRS[55–56], and nebulized antibiotics result in longer infection-free periods compared to standard oral and intravenous antibiotics[57].

Topical tobramycin is a common topical antibiotics used to treat CRS. Aerosolized forms of this antibiotic were initially used in the treatment of pseudomonal pulmonary infections in

cystic fibrosis (CF) patients. Studies of tobramycin nasal irrigations in CF suggest reduction in the likelihood of repeat sinus surgery[56] and improvement in outcome scores[58]. Mupirocin is a topical antibiotic that is effective against Gram-positive bacteria, including Methicillin-resistant Staphylococcus aureus (MRSA). It displays very high levels of activity against Staphylococcus aureus even in nasal secretions[59], and possibly has anti-biofilm activity in vitro[60]. Muporicin is most often employed in patients with Staphylococcus aureus -related CRS who have failed medical or surgical therapy[61–62]. A growing concern is the development of mupirocin resistance, and mupirocin-resistant strains of MRSA may make the topical use of mupirocin obsolete in the future.

Antifungals

A subset of patients with CRS has evidence of fungus in the sinonasal tract, although a consistent role in disease pathophysiology is not well established. In allergic fungal sinusitis, fungal elements are believed to underlie an IgE-mediated hypersensitivity that drives the eosinophilic inflammatory process. Antifungals have been suggested as systemic or topical preparations when fungus-related sinus inflammation is suspected. Since systemic antifungals have significant side effects that involve the liver and kidney, topical antifungals are more often advocated as a form of treatment for CRS[63]. There is conflicting literature on the efficacy of topical antifungals. Ponikau *et al.* showed a benefit of intranasal amphotericin B in double-blinded randomized control trial[64]. Others have not been able to replicate these findings, and found no benefit of topical antifungals[65–68]. A Cochrane study also found no evidence to support the use of antifungals in CRS[69], however there was significant heterogeneity of the surgical state, delivery technique, and medication concentration in the included studies. Amphotericin B dosage in the literature has ranged from 100 ug/ml to 300 ug/ml[69]. The Food and Drug Administration (FDA)-approved concentration is 100 ug/ml, but Shirazi *et al.* showed that concentrations of at least 200 ug/ml are needed for fungicidal activity in vitro[70].

Other agents

Surfactant—Surfactants are compounds that lower the surface tension of liquids and are thought to improve mucocilliary clearance by reducing the adherence of mucus to the epithelial layer. Surfactants can also interfere with microbial cell membrane permeability and disrupt cell membranes. Of recent interest, surfactants have been suggested to have a preventive role against bacterial biofilm formation[71–72]. There are many commercially available surfactant products on the market. Treatment with Johnson & Johnson baby shampoo (a combination of PEG-80 sorbital laurate, cocamidopropyl betaine, sodium trideceth sulphate) at 1% concentration has demonstrated improved patient symptom scores in the treatment refractory CRS[72]. Citric acid/zwitterionic surfactant (CAZS) has been investigated in animal studies and has showed to be effective at reducing biofilms[73]. In addition to its mucolytic and antibiofilm properties, a recent cadaver study showed that when combined with surfactant, saline irrigations improved penetration into non-operated sinus ostia[74].

There is limited literature investigating the safety of topical surfactants. Chiu *et al.* demonstrated that topical surfactant did not cause any significant damage to the cilia or epithelial cells after a short exposure in murine nasal explants[75]. However, a rabbit study using CAZS demonstrated a temporarily denudement of the respiratory cilia[76]. Clinically, patients have complained of minor side effects of nasal and skin irritation, but there have been no serious adverse side effects reported in the literature[72]. There have been anecdotal reports of olfactory dysfunction associated with prolonged use of one commercial surfactant product, leading to temporary withdrawal from the market and subsequent patient warnings.

Further investigations are needed to examine the consequences from supraphysiologic exposure to surfactant.

Natural & Homeopathic Agents: Manuka honey and phytopharmaceuticals— Manuka honeys derived from the floral source in tea trees (*Leptospermum spp*) in New Zealand has recently been described as a natural, inexpensive, and non-toxic topical therapy for CRS[77]. The benefit of Manuka honey is suggested to derive from antimicrobial activity against a broad spectrum of grampositive and gram-negative bacteria in their planktonic states[78–79] and potentially against biofims[80]. Methylglyoxal (MGO), a derivative from the manuka flower, is thought to be the main antimicrobial agent, with honey potentiating its effects through an unknown mechanism[81]. In-vivo studies are needed to determine clinical efficacy. Phytopharmaceuticals are compound medications composed of numerous herbal products. Reports from Europe have reported the use of phytopharmaceuticals to treat sinusitis[82–83]. No clear evidence exists for these alternative therapies, and thus counseling homeopathically-biased patients is important.

New and Future Directions

Further refinement of intranasal drug delivery will demand increasingly sophisticated delivery devices and techniques. Currently, topical drug delivery methods are optimized in cadaveric models or by employing dyes and radioisotopes to study drug penetration in live human subjects. Advances in computer modeling capability now allow detailed experiments of sinonasal drug penetration to be performed *in silico*[84]. At this time, such computer-aided models cannot accurately reflect physiologic factors inherent in CRS, however. In the laboratory, human sinonasal epithelial cell cultures have been advanced as a model system to study cellular and molecular mechanisms affecting topical drug delivery[85]. There is still great potential in U.S. market for intranasal drug delivery given the shortcomings of current products and the challenges with drug delivery devices. Together, the integration of anatomic and physiologic models along with the growing market demand will pave the way for future research and provide the best information on topical drug delivery to the sinonasal cavities.

Ideal characteristics for delivery devices include accurate and repeatable dosing, consistent delivery to targeted site, patient-independent actuation, and effective compliance monitoring[86]. Ideal characteristics for the medication include prolonged mucosal contact time, high local absorption, and minimal depletion[5]. Newer drug delivery strategies, such as drug-eluting stents, are addressing the shortcomings of existing nasal aerosol delivery techniques. The promise of liposomal and nanoparticle technology may yield devices for human trial for the treatment of CRS in the near future.

Drug-Eluting Stents

Stents allow for the slow release of topical drugs at targeted sites, and have been reported for use in the paranasal sinuses since the early 2000s. In animal models, drug-eluting stents have shown decreased granulation tissue without any epithelial damage, decreased post-operative osteoneogenesis and stromal proliferation, and negligible systemic absorption[87–88]. Most drug-eluting stents have focused on corticosteroids, but antimicrobial-eluting stents have also been described[89–90]. The Relieva Stratus Spacer (Acclarent, Menlo Park, California), introduced in 2009, is a non-bioabsorbable stent designed for the ethmoid cavity. The device is approved for saline, however, in an attempt to deliver corticosteroid, physicians have placed triamcinolone into the device reservoir. Investigations have revealed that the device eludes 0.3 ml of triamcinolone acetate 40 mg/ml over 2 to 4 weeks[91]. Approved by the FDA in 2011, the Propel sinus implant (Intersect ENT, Palo Alto, California) is a newer bioabsorbable implant that self-expands in the sinus cavity and

releases 370 μg of mometasone furotate over 4 weeks[92]. Prospective double-blinded trials on a bioabsorbable drug-eluting stent used after ESS in patients with CRS have shown significantly reduced inflammation and prevention of significant adhesion compared to a control stent[92]. One critique of the current stents on the market is that the total dosage of corticosteroid is low, and may not be sufficient to combat the degree of inflammation, especially in cases of recalcitrant CRS. Designing stents with larger-dosage steroid or longer-duration of drug elution may improve the efficacy of these devices. Drug-eluting stents are a promising new technology in the treatment armamentarium for CRS.

Nanoparticles, Microspheres and Liposomes

Nanoparticles are solid colloidal drug carriers ranging from 10 to 1000 nm in diameter and composed of synthetic, natural, or semi-synthetic polymers encapsulating the drug molecule; mircospheres are larger versions of these drug-encapsulating polymers that range from 1 to 1000 μm in diameter with most under 200 μm[93]. The major nanoparticle material that has been studied for nasal drug delivery is chitosan. Chiotsan is a biocompatible cationic polysaccharide consisting of N-acetylclucosamine and D-glucosamine units that is produced by the deacetylation of chitin, the main component of crustacean exoskeleton[94–95]. As a drug carrier, chitosan nanoparticles inhibit enzymatic metabolism and thus allow for slow and sustained drug release[96]. Nanoparticles conjugated with vaccines have been developed for nasal vaccination, and the nasal delivery of insulin, heparin, and other proteins via chitosan nanoparticles has been described[93–94, 96]. Liposomes are phospholipid vesicles are composed by lipid bilayers enclosing aqueous compartments that have the advantage of encapsulating molecules of various sizes and solubility profiles to increased membrane penetration[99]. Intranasal applications of liposome have also been reported[97–99]. Although its application for the treatment of CRS has yet to be studied, nanoparticle- and liposome-based delivery devices may represent a future trend for the delivery anti-inflammatory and anti-microbial agents to the paranasal sinuses.

Conclusion

The increasingly central role of topical therapies in the medical management of CRS has been associated with a burst of related research, technology, and commercial products. This interest in topical agents has arisen from decades of experience with endoscopic sinus surgery and a growing recognition of underlying persistent inflammatory processes in surgically recalcitrant CRS. The surgical goals of enlargement of sinus ostia and outflow tracts have thus shifted from a direct reversal of inflammation to a secondary role in improving access for subsequent topical treatments. A summary of the evidence for topical therapies is shown in Table 3. While more evidence is needed to prove the validity of this approach, the critical importance of creating access surgically has been firmly established for sinus delivery using current devices. Pump sprays and nebulizers have very limited sinus penetration in the unoperated state, although it is possible that new procedures and delivery systems will be developed that will not require wide openings into the sinuses. Nasal saline and intranasal corticosteroids continue to be the most studied and commonly employed agents for long-term topical management of CRS. Further research is needed to establish the efficacy of topical antimicrobials and surfactants, and existing delivery systems for these and other agents continue to evolve.

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Table 1

Delivery Techniques

	Positive/High Pressure	**Negative/Low Pressure**
High Volume	Squeeze bottle Bulb syringe Pressurized sprays Pulsatile jet	Neti pot Nasal inhalation
Low Volume	Pump sprays	Drops
	Atomization	Catheter instillation Nebulizer

Table 2

Nebulizer Systems

	Particle Size	Direction	Velocity
Passive-Diffusion Nebulizers (SinuNeb)	Smaller particles (3 μm)	Constant direction	Slower velocity
Vortex-Propelled Nebulizers (ViaNase)	Larger particles (9–11 μm)	Multiple directions	Faster velocity
Pulsating Aerosol Delivery Device (PARI Sinus)	Smaller particles (3 μm)	Aerosol stream superimposed by a pulsation	Very slow velocity (3–6 L/minute)

Table 3

Summary of Evidence for Topical Delivery

	Study	Study Characteristics	Conclusions
Saline	Harvey et al, 2007	Cochrane review; Included 8 RCTs	Saline irrigation is well tolerated; No significant adverse effects; Beneficial effect for treatment of CRS
Corticosteroids	Joe et al, 2008	CRSwNP – Systematic review & Meta-analysis; Included 13 studies; 6 of these used for meta-analysis	Topical steroids decreased polyp size in CRSwNP
	Snidvongs et al, 2011	CRSsNP – Cochrane review; Included 10 RCTs	Topical steroids is beneficial for CRSsNP in symptom control; Adverse effects are minor
Anti-Bacterials	Lim et al, 2008	Systematic review; Included 10 studies (2 RCTs, 2 controlled studies, 5 cohorts, 1 expert report)	Not first-line therapy; Stronger evidence (level IIb) for cystic fibrosis patient; Can use in refractory cases
Anti-Fungals	Lim et al, 2008	Systematic review; Included 4 studies (3 RCTs, 1 cohort)	No evidence for antifungals in CRS
	Harvey et al, 2011	Cochrane review; Included 6 RCTs	No evidence for antifungal in CRS