

# New medical management techniques for acute exacerbations of chronic rhinosinusitis

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In the past 2 years, intranasal nebulized medications have emerged as a widely prescribed treatment for medical management of chronic rhinosinusitis. This represents an innovative and advanced approach to treating acute exacerbations of chronic rhinosinusitis topically. The use of specially formulated medication compounds delivered by unique nebulization equipment is reviewed in the treatment of patients with chronic sinus disease. Scientific data including related upper and lower respiratory literature is included, as well as the important aspects of factors affecting nebulized medication delivery to the sinuses. The benefits, effectiveness, risks, and adverse effects of intranasal nebulized medications are also addressed. A treatment algorithm identifying appropriate use of nebulized medications in the treatment plan for chronic sinusitis patients is then presented in diagrammatic format. *Curr Opin Otolaryngol Head Neck Surg* 2003, 11:27–32 © 2003 Lippincott Williams & Wilkins, Inc.

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Historical treatments for chronic sinusitis have included chronic oral and intravenous antibiotic use with uncertain optimum duration of therapy, and sinus surgery. In the past 2 years, intranasal nebulized medications have emerged as an innovative and widely prescribed treatment for chronic sinusitis. Estimates, based on ear–nose–throat prescription data, are that up to 30% of ENTs who treat chronic sinusitis have prescribed intranasal nebulized medications in the last 24 months. This article will present a treatment plan hypothesis that integrates the prudent use of this emergent treatment modality (Fig. 1). An additional objective is to determine whether nebulized medications of optimal particle size and formulation can reverse the radiographic, endoscopic, and physiologic findings of patients with chronic sinus disease.

We will discuss the use of specially compounded medications for nasal inhalation in the treatment of patients with chronic sinus disease. Scientific data including related upper and lower respiratory literature are included.

We will address possible indications for the use of specially compounded medications for nasal inhalation in the treatment of chronic infectious sinusitis, fungal sinusitis, chronic hyperplastic sinusitis, allergic rhinitis, as well as consideration in the perioperative period for patients who are undergoing sinus surgery. Also addressed are important aspects of the following.

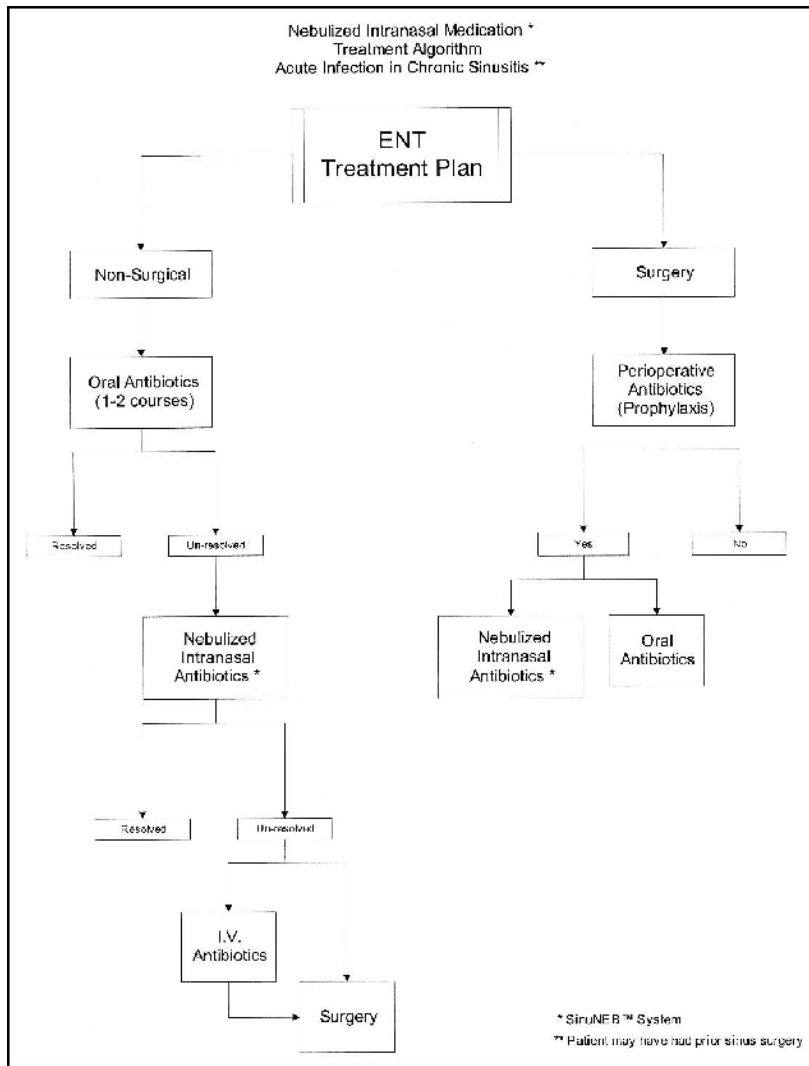
Factors affecting nebulized medication delivery to the sinuses.

Benefits and effectiveness of intranasal nebulized medications.

Risks and adverse effects of intranasal nebulized medications.

## **Nebulized medication delivery factors**

There are two primary factors that affect nebulized delivery of medications to the sinuses. The first factor is the capability of the nebulizer to deliver the optimal particle size [1•] (<5- $\mu$ m aerosol droplets) to permeate the sinus cavities in sufficient concentration to exceed the minimum inhibitory concentration (the lowest drug concentration that inhibits bacterial growth) for most organisms. The second factor is the proper formulation of the selected medications to specific ranges for solubility, stability, pH, osmolarity, and surface tension to achieve effective penetration and deposition. Optimizing both

**Figure 1. Ear–nose–throat treatment plan**

Representation of an algorithm for the treatment of acute exacerbations of chronic rhinosinusitis, including the indications for the use of nebulized intranasal antibiotics.

factors appears necessary to achieve consistently positive clinical results—it seems insufficient to simply combine a drug with solution. The SinuNEB system (distributed exclusively by SinusPharmacy, Carpinteria, CA) was designed to successfully address these two factors. The system provides a specially designed nebulizer combined with proprietary AdhesENT compounded formulations, delivering optimal values of particle size, osmolarity, pH, and surface tension for each compounded medication.

In addition to the primary factors of nebulizer characteristics and medication formulation, there are other aspects that can influence the effectiveness of nebulized medications. These include anatomic issues, pathogen sensitivity to the selected medication, patient compliance, comorbidities such as diabetes, immune compromised states, and renal failure.

### Methodology

The unique nebulizer capabilities were measured using laser particle analysis to identify the aerosol particle size, concentration, and pressure. The efficiency objective is to achieve the highest concentration of emitted particles with diameters in the desired range below 5  $\mu\text{m}$ , from a jet nebulizer [1•]. Results were mass median diameter of 3.22  $\mu\text{m}$ , with 78% less than 5  $\mu\text{m}$ , demonstrating particle emission that is effective for aerosolized medication delivery to the sinuses.

The development of the SinuNEB system with proprietary AdhesENT compounded medications was in direct response to the needs of a substantial patient population that could no longer tolerate repeated systemic antibiotics that failed to deliver proper tissue levels to the affected area of the body (because of decreased blood supply, complicating medical factors, or intolerable side effects). An additional component of the SinuNEB sys-

tem is to provide each patient with an education, compliance, and outcome evaluation program to maximize treatment success.

### Indications for intranasal nebulized medications

Currently, the primary indication (based on historical prescription patterns) for nebulized medications has been therapy for postsurgical acute bacterial infections in patients with chronic sinusitis who have repeatedly not improved with systemic antimicrobial treatment. These are typically the most difficult cases seen. Based on findings from a Stanford University study [2••](three times longer infection-free period with nebulized antimicrobial medication compared with systemic) and a community-based review [3••](82.9% good or excellent response to nebulized antimicrobial medication), it is reasonable to consider nebulized antimicrobial medication early on, after initial oral treatment failure(s) rather than after numerous failures. Nebulized antimicrobial delivery, as a treatment option, is also a consideration before using intravenous antibiotics (Table 1).

Clinical practice guidelines from the American Association of Respiratory Care, for delivery of aerosols to the upper airway [26], describe delivery of therapeutic aerosols to the nose via nebulizers. These guidelines state that in the presence of allergic, nonallergic, and infectious rhinitis; nasal congestion; rhinorrhea; or sneezing or itching of eyes and nose, therapeutic aerosol application may be required. The guidelines also provide outcome assessment parameters as reduced nasal congestion, improved airflow through the nose, reduced rhinorrhea, reduced sneezing, and reduced itching of nose or eyes—of

which nearly all were assessed in each of the above studies [2••,3••].

Intranasal nebulized delivery of antimicrobials may also be a consideration in the pre- and postoperative periods in patients undergoing sinus surgery. Three to 7 days of preoperative use may assist in infection prophylaxis and may improve conditions for surgery. Postoperatively, nebulized antimicrobials may be considered (after surgical packing is removed) for 14 to 21 days, to promote healing, reduce crusting, scarring, and postsurgical adhesions, as well as infection prophylaxis.

The management of airway colonization with *Aspergillus* has not been well defined. However, there is evidence to support an aggressive approach to the recognition and treatment of *Aspergillus* tracheobronchitis with systemic amphotericin or oral itraconazole because it may progress, if untreated, to invasive disease [23].

Aerosolized amphotericin is safe and feasible, but its role in the prevention and therapy of *Aspergillus* infections has yet to be defined. Because established invasive aspergillosis is associated with a high mortality rate, prophylactic postoperative aerosolized amphotericin is used in some lung transplant centers. A study has reported the reduced incidence of invasive aspergillosis using aerosolized amphotericin compared with historical controls [23].

Intranasal application of amphotericin B is described by the Centers for Disease Control and Prevention as a method to suppress or eliminate *Aspergillus* sp from the upper respiratory tract [24]. Intranasal nebulization of specially compounded amphotericin B can be considered for known or suspected *Aspergillus* sp.

The use of topical intranasal corticosteroids has been documented [25], and its benefits were recognized [27] in the treatment of chronic sinusitis and allergic rhinitis. Likewise, topical steroids have shown value in treating chronic hyperplastic sinusitis [28]. Although metered dose inhalers and spray pumps are convenient, they are often ineffective in delivering an effective dose to the sinus and nasal mucosa. Anecdotal retrospective case studies show that specially compounded betamethasone for nasal inhalation can be consistently effective and may be considered after failure of commercially available nasal steroids. Topical intranasal steroids have also been shown to be of benefit in chronic hyperplastic sinusitis, particularly to maintain improvement after burst treatment with oral steroids [28]. Specially compounded medications for nasal inhalation (betamethasone) may also be a consideration in these cases.

### Intranasal nebulized medication benefits and effectiveness

The advantages of specially compounded medications for nasal inhalation are believed to be (1) their ability to

**Table 1. Bacterial/fungal sinus infections—allergic rhinitis**

Documented beneficial effects	<ul style="list-style-type: none"> <li>• Therapy for postsurgical acute bacterial sinus infections after oral medication failure</li> </ul>
Probably beneficial	<ul style="list-style-type: none"> <li>• Therapy for postsurgical acute fungal sinus infections after selected oral medication failure and before numerous additional trials</li> <li>• Preferred alternative before IV therapy for chronic sinusitis</li> <li>• Persistent allergic rhinitis after failure of conventional nasal steroids</li> <li>• <i>Pseudomonas</i>-cultured sinusitis in patients with cystic fibrosis</li> <li>• Postsurgical infection prophylaxis</li> <li>• Polyposis in chronic sinusitis</li> </ul>
Possibly beneficial	<ul style="list-style-type: none"> <li>• Pediatric chronic sinusitis</li> <li>• Severe asthma comorbid with chronic sinusitis</li> <li>• Nonsurgical alternative therapy for chronic infections</li> <li>• Immune-compromised patients with chronic sinusitis</li> <li>• Renal failure patients with poor intravenous access or complications caused by immunosuppressants and tolerance</li> </ul>

provide (through intranasal delivery) a greater concentration of medications directly into the target organ, the sinonasal cavities, reducing systemic complications; (2) the availability of an additional treatment option for current chronic patients that have not responded to or are unable to tolerate oral and intravenous treatment; and (3) the comprehensive physician and patient service component of the SinuNEB treatment system including patient monitoring and compliance enhancement is an extension of the patient care provided in most ear–nose–throat practices.

In a recent Stanford University study, it was found that postsurgical patients treated with culture-directed nebulized antibiotic therapy demonstrated a significant (300%+) increase in their infection-free intervals compared with oral medications [2••]. Patients also reported substantially reduced incidence of severe side effects, and indicated an overwhelming preference for nebulized over systemic therapy. Similarly, a community practice retrospective analysis found that 82.9% of patients (with a history of sinus surgery) had a good or excellent response from nebulized antibiotic treatment, while experiencing only minor transient side effects [3••].

Additional benefits have been reported in measurements of drug concentration in blood versus sinus mucosa after nebulized drug administration [4], where very low concentration in blood was found compared with high concentration in ethmoidal and maxillary mucosa. Likewise, results of a respiratory study [5] treating pulmonary infections topically demonstrated high sputum concentration of tobramycin after delivery from a PARI (PARI; Midlothian, VA) jet nebulizer. The high peak sputum concentrations were associated with very low serum concentrations.

There appears to be culture-based evidence to support an increased incidence of gram-negative pathogens as an increasingly common bacterial sinusitis factor. It can be postulated that the clinical observations of treating the target pathogens in the lower respiratory airway are relevant to the upper airways. *Pseudomonas aeruginosa* is the most common organism cultured from bronchial secretions of patients with cystic fibrosis–related bronchiectasis, and orally inhaled antipseudomonal antibiotics are a major component of treatment. Infection with mucoid *Pseudomonas* has been associated with accelerated progression of the pulmonary disease among children with cystic fibrosis [6]. It is possible that sinus mucoid *Pseudomonas* can be associated with accelerated progression of sinus disease among patients with chronic sinusitis.

Transient eradication of *Pseudomonas* in the lungs has been observed with aerosolized antibiotics [7,21]. Bacterial density in sputum does not necessarily decrease with antibiotic therapy, yet clinical improvement has been

seen subjectively and objectively in patients treated with antibiotics [21]. This beneficial effect may be explained by the observation that pathogenic sublethal doses of aminoglycosides and ciprofloxacin inhibit the production of *Pseudomonas* virulence factors, including proteases [8,9].

Numerous studies of orally aerosolized antibiotics, especially tobramycin, in patients with cystic fibrosis have shown similar beneficial effects to varying degrees [10•,11–19]. In all but one study, forced expiratory volume and forced vital capacity were improved with reductions in sputum *Pseudomonas* density, frequency of exacerbations, use of intravenous antibiotics, and hospitalizations. The results also suggest that the use of aerosol antibiotics in appropriate settings improve quality of life and may reduce overall healthcare expenditures. Another short-term study [20] demonstrated that 4 weeks of inhaled tobramycin reduced sputum *P. aeruginosa* density. Clinical improvement occurred in most patients whose treatment eradicated or reduced *Pseudomonas* density, whereas no clinical response was seen with placebo or when no change in bacterial density was detected with antibiotic therapy.

### Possible risks and adverse effects of nebulized medications

The predominant adverse effects noted in the Stanford University study [2••] and the community practice review [3••] were minor and transient, and resolved after treatment ended. These included dryness around the nose and lip, cough, and tongue or throat irritation. No patients discontinued treatment because of adverse effects. If the dryness is particularly troublesome, application of an emollient ointment during treatment can be used.

Additionally, it is important to be aware that bronchospasm may occur in some cases, and occasional bronchodilator pretreatment has been prescribed. It has been postulated that preservatives, as well as solution osmolality [28], may induce bronchial hyperresponsiveness. AdhesENT compounded formulations attempt to mitigate both of these factors.

The emergence of resistant organisms with the use of any antimicrobial including topical application is a concern and possible risk. Resistance can be defined as increased minimum inhibitory concentration (MIC), *ie*, increased antimicrobial concentration required to inhibit growth [9]. In the absence of sinus data, recent pulmonary literature on aerosol antimicrobials may be useful, particularly evaluating the long-term use of aerosolized antibiotics in patients with cystic fibrosis-related *Pseudomonas* infection. Although pulmonary aerosol delivery systems are, in general, inefficient, a high concentration of antibiotics has been measured in expectorated secretions from the lungs [5]. These high peak levels are

far above the minimum inhibitory concentration for most organisms, substantially exceeding the parenteral breakpoint for antibiotic resistance [5], with bactericidal activity in spite of an increased minimum inhibitory concentration.

Pulmonary research also reveals that systemic serum levels of antimicrobials are very low during aerosolized, therapy with no nephrotoxicity or auditory impairment being reported [10•,17–19]. Tinnitus was reported more frequently in the tobramycin-treated group (8 of 258 patients, or 3.1%) than in the placebo group (0 of 262) [19]. Tinnitus usually resolves, but it can be severe. Transient voice alterations were also found more frequently in the tobramycin group.

Known *hypersensitivity* to a specific drug is a contraindication for nebulized use of that drug.

Only the SinuNEB system (provided exclusively by SinusPharmacy), utilizing specific drug formulations with specific nebulizer technology, has been evaluated in this article. Treatment outcomes using a nebulizer with differing characteristics or use of non-AdhesENT drug formulations are unknown.

## Conclusions

The safety and efficacy of intranasal nebulized medications has been demonstrated in a Stanford University trial [2••] and a systematic community review [3••], with the following key findings:

- Specially formulated medication compounds delivered through intranasal nebulization are well tolerated.
- 300% increased infection-free periods after AdhesENT formulated intranasal medication treatment compared with prior systemic therapy.
- Otolaryngologist-rated 82.9% good or excellent patient response to AdhesENT formulated intranasal nebulized medications.

Based on these findings, a proposed treatment algorithm for chronic infectious sinusitis, with considerations for nebulized antibiotics, is included in Figure 1.

Specially compounded nebulized antimicrobial treatments are no longer reserved for the most difficult cases of chronic infectious sinusitis. It may justifiably be considered:

- after the early treatment failure rather than numerous failures of an oral antimicrobial;
- before selecting intravenous antimicrobial administration; Perioperatively (before and after sinus surgery); or
- for known or suspected nasal colonization of *Aspergillus* sp (amphotericin B).

Specially compounded nebulized betamethasone may also be considered after failure of commercially available steroid nasal sprays in the treatment of allergic rhinitis, chronic hyperplastic sinusitis, as well as adjunctive therapy to nebulized antibiotics.

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