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OTITIS (DP SKONER, SECTION EDITOR)

The Proposed Usage of Intranasal Steroids and Antihistamines for Otitis Media with Effusion

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Abstract

Purpose of Review To examine the role of allergy medications in the treatment of otitis media with effusion (OME), focusing on use of intranasal steroids and antihistamines.

Recent Findings There has been ongoing controversy regarding the role of allergy in the development of OME. Treatment of OME with medications commonly used for allergic symptomatology has been studied. Proposed treatment options include decongestants, mucolytics, oral steroids, topical steroids, antihistamines, and antibiotics. We begin by evaluating the proposed association between allergy and OME, and then evaluate intranasal steroids and oral antihistamine therapy in the treatment of OME. The role of the adenoid and concurrent nasal symptomatology is also addressed.

Summary The preponderance of data suggests that neither intranasal steroids nor antihistamines improve the long-term clearance of isolated OME and are therefore not recommended. However, data are notably limited with regard to improvement rates in OME in patients specifically with concurrent allergy and/or adenoid hypertrophy. Future studies of medications for OME would ideally incorporate study designs controlling for both allergic rhinitis and adenoid hypertrophy, to better understand the impact of these medications on OME in these subgroups of patients.

Keywords Otitis media with effusion · Eustachian tube dysfunction · Allergic rhinitis · Antihistamines · Intranasal steroids · Adenoid

Introduction

Otitis media and allergic rhinitis are highly prevalent conditions which frequently have a significant impact on quality of life in both children and adults [1–3, 4••, 5]. They also result in substantial healthcare expenditures, encompassing direct costs of $2–5 billion for AR [6••] and $4 billion for otitis media with effusion (OME) [4••]. There has been ongoing controversy regarding the role of allergy in the development of OME, and numerous publications have attempted to better characterize the relationship between these two entities. Multiple hypotheses have been proposed to explain any association, but a definitive mechanism has remained elusive. Assessing the impact of treatment paradigms for OME may also provide insight into understanding the relationship between OME and allergic rhinitis. Our objectives are thus to review the role of allergy in OME, as well as the reasoning and data underlying current recommended guidelines for treatment, with a specific focus on the use of intranasal steroids and antihistamines in OME.

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Otitis Media with Effusion

OME exists on a spectrum that includes eustachian tube dysfunction and tympanic membrane retraction; it can also be associated with chronic otitis media with and without cholesteatoma as well. OME denotes fluid in the middle ear without active infection. Fluid in the middle ear decreases function of the middle ear and tympanic membrane such that patients may experience ear pressure, hearing impairment, or

speech abnormalities, while being spared persistent pain, fever, or malaise.

This highly prevalent condition leads to frequent ambulatory medical care visits in both the pediatric and adult age groups. Considering adults and children in aggregate, it is the sixth most common reason to visit an Emergency Department, and the second most common reason for children under 15 years of age [7]. By school age, about 90% of children have experienced at least one episode of OME [4••, 8, 9]. While OM-related healthcare utilization from 2001 to 2011 has had a downward trend, coinciding with the advent of PCV-13 vaccine, it still occurs frequently [10], and prolonged OME may still occur in adults [11]. For each visit in children, 0.77 visits occur in adults, with a per annum visit rate of over 2 million in those 20 years of age and older [5]. The prognosis for OME is favorable; approximately 50% of episodes resolve spontaneously within 3 months and up to 95% resolution has been described over a 1-year timeframe [12].

OME is commonly diagnosed on otoscopic evaluation upon seeing effusion or air bubbles behind the ear drum. Pneumatic otoscopy is quite sensitive and specific for the diagnosis [13], and tympanometry can also be of great utility. When it shows a flat curve and decreased mobility, it typically indicates OME. Many children will have an air-bone gap on audiometric assessment, although some patients can experience normal hearing despite the presence of fluid in the middle ear. Other patients may have associated hearing loss, vestibular abnormalities, poor school/work performance, behavioral issues, ear discomfort, recurrent acute otitis media, or reduced quality of life, and thus require medical care [4••].

Allergic Rhinitis

Allergic rhinitis is also a prevalent condition that affects one in six people in the USA [2, 3] and has an associated annual cost in excess of $18 billion [6••]. Allergic rhinitis is caused by a type I Ig-E-mediated hypersensitivity response which commonly leads to three major symptoms: sneezing, nasal obstruction, and mucus discharge. Within minutes of allergen exposure, mast cells release inflammatory mediators. Additional symptoms may develop 4–8 h later as eosinophils, basophils, and T-lymphocytes enter the affected tissue. Allergic rhinitis is typically classified as either seasonal or perennial, or as intermittent or persistent [14]. This disorder can lead to high rates of lost work productivity and resultant indirect costs [15]. Pharmacologic treatment of allergic rhinitis does show improvement in work productivity [15].

Role of Allergy in OME

A link between allergy and otitis media was first proposed in 1929, when Lewis et al. identified six patients in which the etiology of OME was presumed to be related to allergy [16]. Since then, there have been many attempts to better characterize the relationship between OME and allergy. Multiple hypotheses exist to explain this association, including various molecular mechanisms and inflammatory processes as well as the similarities of the histology, but a definitive mechanism yet to be identified. This has led to continued controversy regarding the presence of a veritable connection.

The unified airway starts at the nasal vestibule and includes the paranasal sinuses, middle ear cavity, pharynx, and laryngeal structures. These are all lined by the same pseudostratified ciliated columnar epithelium with mucous secreting goblet cells. These specialized linings help transport secretions throughout the upper airway including from the nasal cavity and middle ear cleft into the nasopharynx with rhythmic ciliary beats.

The unified airway theory describes that the respiratory tract including the nose, sinuses, middle ear, and pulmonary tree may behave as one integrated unit. Disease processes may initially involve only one unit, but over time, can expand to involve other areas of the upper airway. This concept has increased awareness of the relationships between varying portions of the airway. It is now recommended that when evaluating one part of the airway, it is prudent to also evaluate the other portions of the functional unit. For example, when evaluating a patient with asthma, an upper airway evaluation should be at least be considered [17]. This concept applies to our analysis of allergic rhinitis and OME as these pathophysiologic diagnoses may in fact be related to other aspects of the unified airway, given that the nasopharynx connects the middle ear, nose, and lymphoid structures.

Role of the Adenoid

The adenoid is an aggregation of lymphoid tissue in the nasopharynx. Adenoid size increases rapidly until approximately 6 years of age, and then growth slowly plateaus over the next few years [18]. Around puberty, regression of the adenoid occurs, such that the adenoid is typically involuted by young adulthood [19]. The adenoid is organized in germinal centers, supporting its role as a lymphoid structure. It may thus have an immunomodulating function.

When the adenoid is enlarged, it can lead to symptoms such as nasal obstruction, snoring, mouth-breathing, and hyponasal voice. Because the adenoid lies near the eustachian tube orifice, an adenoid problem can increase the likelihood of eustachian tube dysfunction and subsequent OME [20]. However, not all children with adenoid hypertrophy develop OME, such that beyond mechanical obstruction, there is a possible role for local inflammatory mediators or biofilm formation as a potential link between eustachian tube dysfunction and adenoid hypertrophy [21].

Studies have shown that children with OME have higher levels of histamine and subepithelial mast cells in their adenoid tissue compared with children without OME [22–24]. Interestingly, while chronic rhinitis and OME are both common in children with adenoid hypertrophy, combined nasal cytology and skin prick testing could not identify a statistically significant association with allergic rhinitis in Quaranta's analysis [22]. Another evaluation of mucociliary clearance in subjects with adenoid hypertrophy with and without OME showed decreased mucociliary clearance time and velocity in the group with both OME and adenoid hypertrophy compared with the group with adenoid hypertrophy alone [20]. Moreover, there was improvement in both mucociliary clearance time and velocity following adenoidectomy ± tympanostomy tube placement. However, improvement occurred regardless of the pre-operative adenoid size, supporting a role beyond that of mechanical blockage [20].

Intranasal steroids have been shown to decrease symptoms of nasal blockage, rhinorrhea, cough, snoring, and quality of life in patients with adenoid hypertrophy [25]. While this same analysis did not show an improvement of adenoid size on nasal endoscopy, a subsequent study by Bhargava et al. did show improved choanal obstruction following intranasal steroid therapy [26]. These studies did not, however, address OME. A follow-up study by Bhargava did subsequently make a connection between this alteration in choanal obstruction and OME [27].

Treatment Options

Patients with OME and/or allergic rhinitis may require no specific treatment if symptoms are self-limited or mild. Many proposed treatment options have been considered for patients with OME including decongestants, mucolytics, oral steroids, topical steroids, antihistamines, and antibiotics. Non-medication treatments include tympanostomy tube placement, auto-insufflation, myringotomy, and adenoidectomy. However, the efficacy of many of these treatment options has been questioned. Results of these analyses are published in Cochrane Reviews and multiple societal guidelines [4••, 6••, 8, 28, 29], though wide variation in treatment strategy is often seen. We will next focus specifically on the data surrounding the treatment of OME with antihistamines and intranasal steroids.

Intranasal Steroids for Otitis Media with Effusion

Reducing edema in the nasopharynx at the site of the opening of the eustachian tube has been proposed as a logical method to improve eustachian tube dysfunction and potentially OME. Intranasal steroids are considered safer than their oral counterparts since the glucocorticoid is rapidly degraded within the nasal mucosa to less active metabolites, such that only a small percentage is absorbed systemically [30–32].

Adverse effects of topical steroids include stinging, epistaxis, dry throat, and worsening eye disease. Suppression of the hypothalamic-pituitary axis has also been evaluated, though most clinically relevant doses did not lead to HPA axis suppression [27]. Additionally, the incidence of epistaxis related to intranasal steroid sprays is quite low, ranging from 2 to 12% [27, 33].

For the Use of Intranasal Steroids for OME

Several analyses have evaluated the role of intranasal steroids in OME and described a potential benefit in their use of treatment for this common pathology. In 1998, Tracy and Demain concluded that intranasal steroid therapy was a helpful adjunct in management of middle ear effusion [34]. This double-blind, placebo-controlled study compared the effects of prophylactic antibiotics alone or in combination with intranasal beclomethasone or placebo on middle ear pressure, otoscopic exam, and symptom scores in children with persistent middle ear effusion (> 3 months). Subjects in the beclomethasone plus antibiotic group improved more rapidly than those in the antibiotic alone or the placebo group in the initial 8-week treatment period. At 12-week follow-up, this combination treatment group was the only group to show improved tympanic pressure in both ears. Improvements in symptom scores at 12 weeks were also better in this combination therapy group ($p = 0.008$) [34]. No differences were seen in this study between subjects with and without allergy [34]. The authors concluded that intranasal steroids were an option for some parents who were hoping to avoid surgery for their children [35]. However, follow-up beyond the 12-week study duration was lacking.

In 2002, Butler et al. then reported that both topical and intranasal steroids alone or in combination with an antibiotic lead to quicker resolution of OME in the short term, but that this effect did not sustain in the long term [28]. However, as discussed further below, this analysis was then updated by Simpson et al. in 2011, who did not show the same effect even in the short term with topical steroids alone, thus raising further controversy on this issue [12].

A small study by El-Anwar et al. compared the treatment of OME with topical mometasone for 3 months, oral prednisolone, and nasal saline spray. Sixty patients were included in this analysis, and while the examiner was blinded as to the type of treatment, the patients were not blinded and randomization strategy was not clear. Clinical findings including retraction, lack of luster, and fluid/air bubbles behind the TM were evaluated as was tympanometry. All clinical measures improved in the oral and topical steroid groups, while no significant change was noted in the placebo (nasal saline spray) group over the 6-month follow-up period [36]. No significant

differences were noted in the treatment effect of steroid nasal spray and systemic steroids ($p = 0.21$). These authors thus concluded that there may be some benefit to treatment with intranasal steroid spray in patients with OME when treatment is extended for a 12-week period.

Intranasal Steroids and the Overlapping Impact on the Adenoid and Allergy

Given the perception of the potential link between allergic rhinitis, adenoid hypertrophy, and OME, some studies have explored whether patients with both OME and allergic rhinitis would benefit from intranasal steroids targeting the inflammatory component of allergic rhinitis [35, 37]. For example, a prospective, randomized but unblinded study of children with adenoid hypertrophy with and without OME who were awaiting adenoidectomy ± tympanostomy tube placement received either mometasone furoate nasal spray or no medical intervention. Rates of atopy were not different between the treatment and placebo group (8.9% study group, 9.0% control group). The patients treated with intranasal mometasone experienced higher resolution rates of OME at 6-week follow-up compared with control subjects (42.2% vs. 14.5% resolution rate; $p < 0.001$) [37]. While this result was independent of atopy ($p = 0.607$ in treatment group and $p = 0.377$ in control group), the size of the adenoid also decreased in this group. This reduction in adenoid size was seen more significantly in those with atopy than without [37]. A follow-up study by the same group showed lasting efficacy at the 12-month follow-up. Of those who initially postponed surgery, only one subject underwent delayed adenoidectomy. Only 2 cases of OME recurred, both of which responded to a second course of nasal steroids [38]. Therefore, it does raise question as to whether the treatment of the allergic inflammation in these subjects affected the results or whether these results would have been seen with the OME and adenoid alone. This study suggests a potential role for intranasal steroids, but it is unclear whether any effect arises from an impact on allergic rhinitis, the adenoid, or both.

Also taking into account the size of the adenoid, a 2014 study by Bhargava et al. evaluated whether mometasone used intranasally would affect rates of OME resolution. This prospective randomized double-blind placebo-controlled study evaluated children with grade 3 or 4 adenoid hypertrophy with persistent OME for more than 3 months. One group received mometasone for 6 months, while the control group received saline nasal spray for the same time period. Resolution of OME was significantly higher in the study group when compared with the control group (28/30 compared with 16/32, $p = 0.0004$) [27]. However, this study did not exclude subjects with allergic rhinitis, nor have a delineated subgroup with allergic rhinitis. Thus, the extent to which allergy vs. the adenoid affected these findings is yet to be established. The most recent clinical practice guideline for the treatment of otitis media with effusion, which was endorsed by the American Academy of Head and Neck Surgery Foundation and the American Academy of Family Physicians, describes adenoidectomy as an option to treat chronic OME in children 4 years of age and older as direct intervention for the adenoid may impact OME [4••].

Future studies of intranasal steroid use for OME would ideally incorporate study designs which control for both allergic rhinitis and adenoid hypertrophy, as both may be affected by this class of medication [26, 39••] and both may have an impact on OME [27, 40–42].

Against the Use of Intranasal Steroids

Beyond the adenoid considerations above, there is substantially more evidence which demonstrates that intranasal steroids are not effective in treating OME. These studies differ from the above analyses as most evaluate the efficacy as monotherapy as opposed to combination therapy. In 2009, a double-blind randomized placebo-controlled trial of 3 months of topical intranasal corticosteroids in 4–11-year-old children with bilateral otitis media with effusion evaluated 217 children presenting to primary care practices within the UK. The proportion of children cleared of OME was assessed at 1-, 3-, and 9-month timepoints. At 1 month, 40.6% had achieved clearance of OME as determined by return to type A or C-I tympanometry, compared with 44.9% of the placebo group (adjusted odds ratio 0.93, CI 0.50–1.75). At 3 months, 58.1% of the steroid group had resolved compared with 52.3% of placebo group (AOR 1.45, CI 0.74–2.84). At 9 months, 55.6% of treatment group remained clear while 65.3% of the placebo group remained clear (AOR 0.82, CI 0.39–1.75). The authors therefore concluded that topical intranasal corticosteroids were unlikely to be clinically effective treatment for OME in the primary care setting [43]. One issue raised regarding this study was the proportion of patients with mild disease which may be likely to resolve spontaneously. Therefore, this study did try to assess tympanometry performed 3 months apart; however, many subjects did not ultimately undergo this second analysis. A follow-up meta-analysis by Williamson in 2011 similarly showed that pooled data from multiple RCTs did not show a significant benefit of intranasal corticosteroid therapy over placebo in the treatment of OME. The rates of resolution and rates of reduced persistence of effusion at 3 weeks were not significant [44]. No severe or lasting adverse events were noted and there was no statistically significant increase in stinging, nosebleeds, cough, or dry throat in the included trials [44]. While it appears that some studies tried to collect information about atopy, no clear subgroup analysis was able to be completed with regard to atopy or adenoid hypertrophy in these investigations.

Additionally, cost-effectiveness of topical nasal steroids for the treatment of OME was evaluated by Petrou et al. in 2010, using the results from Williamson's study (above). As mentioned previously, tympanometric cure rates were found between the topical steroid and placebo groups (40.6% vs. 44.9%; AOR 0.934, CI 0.498–1.751, $p = 0.831$) in this analysis. The probability of topical steroid therapy being cost effective was 24.2% at 20,000 £ /QALY threshold and 23.9% at 30,000 £/QALY threshold, concluding that topical steroids were unlikely to be cost effective [45].

A prospective, double-blind, randomized, placebo-controlled trial by Gluth et al. evaluated the effect of triamcinolone acetonide topical nasal spray on eustachian tube dysfunction and related signs including OME and negative middle ear pressure. Both adults and children were included in this analysis. No difference was noted in the post-treatment symptom scores or in the rates of normalization of previously abnormal tympanometry. This was evaluated on both a per patient (19% vs. 32%, $p = 0.18$) and per ear (22% vs. 35%, $p = 0.15$) basis, with neither method showing statistical significance [46]. This study did not control for the presence or absence of allergic rhinitis in its analysis.

A meta-analysis by Simpson et al. in 2011 evaluated 945 subjects across 12 studies (all prospective, randomized and controlled) with OME. Use of oral and topical steroids, either alone or in combination with antibiotic, was evaluated for efficacy in treatment of hearing loss associated with OME. No benefit was noted for the use of intranasal steroids (either alone or with antibiotics) at any time period [12]. While there was some improvement in hearing loss resolution on short-term follow-up (< 1 month) with oral steroids (with or without concurrent antibiotics), this effect was not persistent when evaluating follow-up at > 1 month. Allergy status and the status of the adenoid were not evaluated in this analysis.

In 2013, a panel evaluated comparative effectiveness of treatment options for OME. This group hoped to build on the prior work on this topic by pooling the data of prior work to compare treatment strategies of OME in terms of efficacy, effectiveness, and comparative effectiveness. They concluded that intranasal steroids did not show differences in cure rates at various follow-up points when used alone or in conjunction with antibiotics [47].

One interesting feature of these studies is that there is significant heterogeneity in the published data as to the inclusion of subjects with allergy/atopy, adenoid hypertrophy, and nasal symptoms. When included, some studies require more objective results with skin-testing data while others evaluate allergic status by history alone. Similar situations arise for adenoid hypertrophy and nasal symptomatology. Cengel's and Petrou's analyses are the only studies to address both of these factors as subgroup analyses (see Table 1) [37, 45]. Thus, at present, there seems to be insufficient data to address the question of whether response of OME to intranasal topical corticosteroids is different in a subgroup of patients with pre-existing allergy, adenoid hypertrophy, and/or nasal symptoms.

Alternative Applications of Intranasal Steroids

The above studies are all completed using topical intranasal steroid in spray application. These low-volume, low-pressure sprays are well tolerated, but most medication only reaches the anterior nasal cavity [48, 49]. Other forms of topical intranasal steroids have now been more commonly used in an "off-label" manner. These various applications are now commonplace in clinical treatment for adult patients with chronic rhinosinusitis and include topical intranasal steroid irrigations, concentrated intranasal drops, and an exhalation delivery system application. For example, a study in 2008 by Kanowitz et al. showed that budesonide administered via nasal mucosal atomizer device leads to improved symptoms scores and less tendency for need for oral steroid therapy in patients with chronic rhinosinusitis in the post-surgical period [50].

Many of these alternative application systems are being used as they are felt to penetrate further into the sinonasal cavity. This approach allows drug delivery to the targeted area more readily [51], and therefore raises the question as to whether the lack of overwhelming evidence to support treatment of OME with topical low-volume intranasal steroid spray could be due to lack of delivery of the medication to the posterior aspects of the nose, sinonasal cavity, nasopharynx, and eustachian tube orifice. A potential avenue for future research could be to evaluate whether improvement in OME is seen with higher volume steroid irrigations or alternative topical steroid delivery systems, which could penetrate further past the nasal valve area and anterior nasal cavity.

Oral Antihistamines for OME

Given the potential allergic inflammatory component of middle ear effusion, questions have been raised as to the potential treatment of OME with antihistamines. It has been proposed that antihistamines could decrease congestion of mucous membranes and therefore decrease obstruction of the eustachian tube. It has also been proposed that if eustachian tube dysfunction was in part caused by allergy, then treatment of allergy with use of an anti-allergy antihistamine medication would allow for better function and perhaps improvement in related symptomatology.

Histamine acts primarily through H1 receptors leading to increased venule permeability, smooth muscle contractions, increased nasal mucous production, and neutrophil and eosinophil chemotaxis [7, 52]. Antihistamines block this action, acting as an inverse agonist. Multiple types of antihistamine

Table 1 Intranasal steroids for OME evaluation of subgroup analyses

Authors	Year	Study design	Allergy status	Adenoid/nasal status
Supporting use:				
Tracy and Demain et al.	1998	Prospective double-blinded placebo-controlled RCT	Assessed via skin testing—found on difference between groups and no association on subgroup analysis	Not assessed
Butler et al.	2002	Review of RCTs	Not assessed	Not assessed
El-anwar et al.	2015	Prospective single blinded	Not assessed	Not assessed
Cengel et al.	2006	Prospective unblinded RCT	Assessed via skin testing—found no difference between subgroups in atopy analysis for OME	Assessed adenoid/choanae ratio—found ratio decreased more in atopy group and treatment group
Bhagava et al.	2014	Prospective double-blinded placebo-controlled RCT	Not assessed	Assessed—found improvement noted in treatment group
Against use:				
Wiliamson et al.	2009	Prospective double-blinded placebo-controlled RCT	Assessed via history alone—found no statistically significant difference between groups (subgroup analysis with statistically significant difference only at 3 months	Not assessed
Williamson et al.	2011	Meta-analysis/systematic review	No clear subgroup analysis	Looked at adenoidectomy but not in context of steroid therapy
Petrou et al.	2010	Prospective double-blinded placebo-controlled RCT	No significance on subgroup analysis	Only symptoms pertaining to adenoids assessed
Gluth et al.	2011	Prospective double-blinded placebo-controlled RCT	No subgroup analysis	Not assessed
Simpson et al.	2011	Systematic review	Not assessed	Not assessed
Berkman et al.	2013	Systematic review	Not assessed as subgroup	Not assessed as subgroup

medications exist. While first-generation antihistamines have remained commonly utilized, the newer second-generation antihistamines have a higher selectivity for histamine receptors and also lack anticholinergic activity. The antimuscarinic action is often less desirable as it is partially responsible to the drying of airway secretions and sedative effects. It may also lead to epithelial dysfunction by decreasing ciliary beat frequency and increasing the viscosity of mucus [7]. Thus, second-generation agents may allow for selective histamine blockage to achieve decreased release of cell mediators from mast cells, reducing epithelial inflammation while minimizing the thickening of mucus. Side effects of antihistamines include, but are not limited to, sedation, nervousness, hyperactivity, dry mouth, diaper rash, seizures, blood pressure variability, increased urine output, and gastrointestinal upset [53, 54]. Thus, it is important to determine whether the potential efficacy of these treatments warrants the risk of side effects.

For the Use of Antihistamines

The data supporting antihistamine use for OME is sparse and largely relates to animal studies. When instilled locally through a tube, hydroxyzine reduced the amount of histamine present in the middle ear effusion and decreased the frequency of relapses of OM [55]. Animal studies showed azelastine hydrochloride improved elimination of MEE in guinea pigs with both OME and allergic rhinitis, but this was felt to be an indirect action by affecting nasal symptoms [56]. A more recent analysis of the allergic rat with otitis media showed that ototopical antihistamines may be effective in treating patients with allergy-induced eustachian tube dysfunction [52].

Given that side effect profiles for second-generation antihistamines are less than first-generation antihistamines, Goodrich et al. raised the question as to whether these second-generation medications may have increased efficacy and better side effect profiles for the utilization of these medications for OME [7].

Against the Use of Antihistamines

Similar to the analysis of intranasal steroid medications, there is a plethora of convincing data advising against the use of antihistamines in treatment of OME. A meta-analysis and systemic review by Griffin et al. in 2006 and updated again in 2011 showed

no statistical benefit of treatment with antihistamine, decongestant or antihistamine, and decongestant combination therapy for OME when using persistence of OME as the main outcome measure [13, 57]. Combined decongestant-antihistamine therapy showed no benefit in treatment of OME with RR 0.97 (CI 0.89–1.04) [13, 58]. Additionally, an increased rate of medication side effects was seen in this analysis; with treated subjects experiencing 11% more side effects than untreated subjects (NNT = 9) [13].

There has been concern raised that antihistamines, in addition to being ineffective in the treatment of OME, may even prolong the duration of effusion [53]. It was felt that possible inhibition of eustachian tube function by reducing mucociliary function and anticholinergic properties. For example, these medications may increase the viscosity of the middle ear fluid thus affecting drainage and absorption [54, 58]. Though Coleman's study was geared towards patients with acute otitis media (AOM), some of the studies included in the analysis did evaluate OME. In this updated review, antihistamines were not recommended for treatment of AOM.

Another meta-analysis by Williamson's group also evaluated the rates of resolution of effusion and persistence of effusion at 4 and 12 weeks. The rates of improvement of OME compared with placebo were not statistically significant. Moreover, there were reported adverse effects (RR 2.54, CI 1.76–3.67) favoring treatment with placebo over antihistamine therapy [44]. Studies in this analysis did include antihistamine-decongestant combination therapy, which raises some question as to whether results would vary with antihistamine treatment alone, particularly in the adverse events rates.

Berkman's 2013 analysis did not even include antihistamine use in the comparative effectiveness analysis, stating that extensive prior review showed no benefit in this population [47].

A small study by Ertugay et al. assessed levocetirizine, montelukast, or the combination of both compared with placebo in the treatment of OME. Improved otoscopic scores in the combination therapy group were noted ($p < 0.05$), but there were no significant changes in tympanometry findings. Moreover, the levocetirizine alone group seemed to perform worst among the treatment groups [59]. Thus, while some improvement was noted in the group receiving combination therapy, there was no significant improvement relative to placebo when evaluating use of levocetirizine alone. This study did question whether higher doses of the antihistamine would have led to different results.

Similar to the data surrounding intranasal corticosteroids, the literature evaluating antihistamine use in subjects with OME does not provide targeted subgroup analysis of patients who have clearly defined atopy. Additionally, the studies on antihistamine usage do not routinely assess nasal symptoms or adenoid hypertrophy in their analyses (see Table 2).

Subgroup Data

It is important to assess the relative improvement rates of OME in patients with and without allergy and/or adenoid hypertrophy to better understand this disease process and treatment implications. In the majority of the studies performed to date, there is minimal data with formal subgroup analyses of patients with nasal symptoms, atopy, or formally diagnosed adenoid hypertrophy. Goals of intranasal corticosteroids and antihistamine therapy are to address inflammation and histamine release leading to inflammatory-based symptoms and tissue hypertrophy/edema. Thus, if the study medications are provided only to subjects with limited inflammation, it may be that there is no true target available for therapy. In other words, it may be that only subgroups with significant allergic history or atopic status (or significant adenoid hypertrophy and nasal obstructive symptoms) may achieve treatment benefit with these medications. As shown in both Tables 1 and 2, most studies performed to date do not perform a subgroup analysis on these patients. In those that did seek to evaluate this, numbers of included subjects and significant heterogeneity in the definition of the subgroup may affect the results. Further research in this area may help to better identify better understanding of the role that allergy may play in the development and treatment of OME.

Adherence to Guidelines

The preponderance of data suggests that neither antihistamines nor intranasal steroids hasten the clearance of isolated OME and are therefore not recommended in this circumstance [4••, 8, 29, 60]. Intranasal steroids are unlikely to be beneficial although risks are low, while antihistamines are both not beneficial and may even be harmful. The 2016 update to the clinical practice guideline for otitis media with effusion makes strong recommendations against the use of topical intranasal steroids or antihistamines for treating OME in the absence of other concomitant conditions. It also notes, "In patients with concomitant OME and allergic rhinitis, there may be a role for topical intranasal steroids, since they do target the inflammatory component of allergic rhinitis, which may be a contributing factor to OME." [4••] Although antihistamines are not recommended for OME, the guideline does mention that they may help with improvement of nasal and ocular allergic symptomatology that is often seen in the subgroup of patients with OME who also suffer from allergic symptomatology [4••]. These guidelines also recommend that for children 4 years of age or older, adenoidectomy should be considered [4••]. Adenoidectomy should not be performed for patients younger than 4 years of age unless a distinct indication (nasal obstruction, chronic adenoiditis) exists.

It is also of interest to know whether these above recommendations are being followed in our clinical practices. While intranasal steroids are not recommended for isolated OME, a

Table 2 Antihistamines for OME evaluation of subgroup analyses

Authors	Year	Study design	Allergy status	Adenoid/nasal status
Supporting use:				
Goodrich	2009	Review	Not assessed	Not assessed
Against use:				
Chonmaitree et al.	2003	Prospective double-blinded placebo-controlled RCT	Not assessed	Not assessed
Griffin et al.	2006	Systematic review	Planned but then not assessed	Not assessed
Coleman et al.	2008	Systematic review	Planned but then not assessed	Not assessed
Griffin et al.	2011	Systematic review	Planned but then not assessed	Not assessed
Williamson et al.	2011	Meta-analysis/systematic review	No clear subgroup analysis	Evacuated adenoidectomy (but not in the context of antihistamine therapy)
Ertugay	2013	Prospective double-blinded placebo-controlled RCT	Not assessed	Not assessed
Bonney et al.	2014	Review	Not assessed	Not assessed

large study by Wang et al. in 2017 showed that intranasal steroids were prescribed in 10% of visits in which OME was diagnosed compared with 3.5% of visits in which OME was not diagnosed (univariate OR 3.07, CI 1.85–5.08) [61••]. Similarly, in 2015, Prince et al. showed that antihistamines were used in 9.5% of OME visits as opposed to 5.5% of visits without OME (OR 3.53, CI 1.62–7.71) [62]. When evaluating these data together, it was demonstrated that 115,800 pediatric visits per year resulted in excess antihistamine usage and 134,020 visits per year were associated with potentially excess intranasal steroid use. These patients were therefore exposed to potential adverse effects from these medications while likely receiving no significant benefit in hearing, risk of further surgery, or OME resolution [63••]. These potentially inappropriate prescribing patterns can also lead to excess cost. For example, the annual cost of prescribed medications with visits associated with acute or chronic eustachian tube dysfunction in adults exceeded $8.5 million (mean of $80.78 per patient who filled a prescription) [64••].

Within US practices, the patterns of medication administration for OME varied with practice type [63••]. Antihistamine prescription administration was higher in the emergency department setting than in the non-emergency department setting (although both showed high rates of antihistamine use when OME was present) [63••]. However, intranasal steroid use was higher outside the emergency room. Visits to an otolaryngologist were not associated with increased antihistamine or steroid administration [63••]. These variations in practice patterns offer a unique opportunity to target education materials to individual practice setting types according to the prescribing observations. As we strive to provide effective and high-quality care for our patients, these issues are important to consider. It is of utmost importance to introspectively assess our own practice patterns for areas where we could improve. This may allow us to reduce inappropriate prescribing and health care utilization costs, while improving patient safety.

Conclusions

Otitis media with effusion and allergic rhinitis are highly prevalent conditions with a controversial relationship. Some data support an association between these states through eustachian tube dysfunction or through allergic pathophysiology affecting the "unified airway." However, treatments typically offered for allergic rhinitis do not seem to produce a significant effect in treatment of isolated OME as evidenced by the most up-to-date large population studies and current practice guidelines. This includes the use of antihistamines and intranasal steroids, neither of which have been consistently shown to be effective in treatment of OME. Moreover, inappropriate use of these medications may lead to patients suffering from some adverse effects and lead to increased health care utilization cost. However, further research is needed to better understand treatment effects of these medications in the subgroup of patients with clearly concomitant allergic rhinitis, adenoid hypertrophy, and related nasal symptomatology. Awareness of the current guidelines and continued evaluation of our own individual and aggregate practice patterns offers an opportunity for quality improvement and education of our colleagues, with the ultimate goal of providing the highest quality patient care.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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