

# Pharmacotherapy for Allergic Rhinitis

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## KEYWORDS

• Allergic rhinitis • Allergy treatment • Allergy symptom control

## Key Points: ALLERGIC RHINITIS PHARMACOTHERAPY

- AR can be divided into intermittent and persistent symptoms.
- Among the large array of pharmacotherapeutics available for the management of allergic rhinitis, intranasal corticosteroids and oral antihistamines are first line agents for allergic rhinitis.
- Other agents can be added in a symptom-based manner, for example, intranasal anticholinergics for rhinorrhea, intranasal decongestants for nasal obstruction, and intranasal antihistamine for pruritus.
- Anti-IgE antibody is newer class of pharmacotherapeutics that may provide better symptom control as well as downregulate IgE receptors.

Allergic rhinitis (AR) is a very common chronic respiratory disorder thought to be secondary to IgE-mediated type I hypersensitivity of the nasal mucosa to inhaled or, in some cases, to ingested allergens. It affects approximately 15% of Americans and leads to health care costs of two to five billion dollars spent per year.<sup>1</sup> There has been a steady rise in atopic diseases including AR.

AR has also been shown to negatively impact quality of life. Poor sleep quality is associated with AR, and daytime sleepiness can result from antihistamine medications used in the treatment of AR.<sup>2</sup> Decreased concentration in school children has been demonstrated,<sup>3</sup> and studies have shown that AR can lead to decreased productivity. AR is linked to other atopic disease states and is four to six times more likely to develop in those with asthma, which supports the link between the upper and lower airways as described by the unified airway theory.<sup>4</sup> AR, although frequently not life-threatening, can have significant impact on overall health status and daily life of affected individuals.

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AR can be divided into seasonal (or intermittent) and perennial (or persistent). Seasonal AR is commonly known as “hay fever,” although it is not caused by hay and does not present with fever. Perennial AR implicates allergen exposure on a more constant basis. AR has two phases: early-phase and late-phase inflammation. The early-phase reaction occurs usually within minutes and results in symptoms mediated by histamine. Sneezing, pruritus, nasal congestion, and rhinorrhea are some of the early-phase symptoms. Late-phase symptoms stem from eosinophils and T-cell mediated cytokines such as interleukin-4 and interleukin-5 and can present with rhinorrhea and nasal congestion.

Management of AR includes avoidance, pharmacotherapy, and immunotherapy. This article discusses the role of pharmacotherapy and reviews the wide spectrum of pharmacologic options available as well as these agents’ efficacy and safety.

INTRANASAL CORTICOSTEROIDS

Topical application of corticosteroids was introduced in the early 1970s.<sup>5</sup> Intranasal corticosteroids are thought to work mostly locally, thereby avoiding the unwanted side effects that are associated with oral or intravenous corticosteroids such as cushingoid habitus, cataracts, osteoporosis, gastrointestinal irritation, candidiasis, and hyperglycemia, while maintaining the beneficial antiinflammatory effects that corticosteroids offer. The newer formulations of intranasal corticosteroids show even lower amounts of systemic absorption—approximately 1%. There are eight agents available currently for use in the United States (Table 1).

Intranasal corticosteroids are understood to be most effective against late-phase mediators in eosinophilic-dominated inflammation with some effect on the acute phase of the allergic response.<sup>6</sup> These agents are useful controller drugs and, therefore, should be used in a chronic manner. However, there are some data supporting its use on an as needed basis. Newer agents have been reported to have an effect as early as 24 hours after administration; however, the benefit from chronic use still seems to outweigh that of as needed use.<sup>7</sup>

Dexamethasone nasal drops were some of the first used topical corticosteroids. Although topically applied, they had significant adverse effects similar to those of systemic corticosteroids, partly due to its long half-life and the lack of first-pass metabolism in the liver.<sup>5</sup> Subsequent drugs that were first-pass metabolized included beclomethasone, which is the most extensively used in airways. Budesonide,

| Table 1<br>Intranasal corticosteroids: generic and brand names |                           |
|----------------------------------------------------------------|---------------------------|
| Generic                                                        | Brand                     |
| Beclomethasone dipropionate                                    | Beconase Aq, Vancenase Aq |
| Budesonide                                                     | Rhinocort Aq              |
| Flunisolide                                                    | Nasalide, Nasarel         |
| Fluticasone propionate                                         | Flonase                   |
| Mometasone furoate                                             | Nasonex                   |
| Triamcinolone acetonide                                        | Nasacort Aq               |
| <i>Newer</i>                                                   |                           |
| Fluticasone furoate                                            | Veramyst                  |
| Ciclesonide                                                    | Omnaris                   |

fluticasone propionate, mometasone furoate, and triamcinolone acetonide are well studied agents that have even less bioavailability and shorter plasma half-lives than beclomethasone. The newer agents, Food and Drug Administration (FDA) approved in 2006–2007, include ciclesonide and fluticasone furoate.

Most intranasal corticosteroids are poorly lipid soluble, therefore requiring an aqueous solution used in a pump spray to suspend and deliver the drug. There appears to be a dose-dependent response to intranasal corticosteroids. Higher doses result in greater benefit. Overall, the intranasal doses tend to be smaller than those for the lung.<sup>5</sup>

In the treatment of seasonal AR, intranasal corticosteroids are appropriate first-line agents. Studies have demonstrated significant symptomatic relief with the use of intranasal steroids alone.<sup>8</sup> However, for perennial AR, management with sole intranasal corticosteroids has not proven to be as beneficial. Depending on the severity of the disease, short courses of oral corticosteroids, in addition to topical intranasal steroids, improve symptomatic relief more than intranasal steroids alone.<sup>7</sup>

The treatment of AR in children and in pregnant women is very similar to that of nonpregnant adults; however, because of the potential undue consequences in these two populations, practitioners may be advised to be more judicious with the administration of intranasal corticosteroids. Large pediatric studies have not shown significant adverse effects with use of intranasal corticosteroids<sup>9</sup> or significant systemic levels of corticosteroid absorption.<sup>10</sup> In pregnant women, there is always the concern for adverse effects especially to the unborn fetus, particularly cleft lip and palate development. Thus far, there have not been any reported teratogenic effects. Overall, there are not enough studies to support any definitive conclusion regarding the use of these agents in pregnancy. Therefore, careful risk-benefit analysis is recommended for mother and fetus when considering the use of intranasal corticosteroids for the treatment of AR in pregnant women. Of the intranasal corticosteroids, budesonide is the only category B drug.

Patient education regarding how to use these drugs should be highlighted. The correct method to administer a dose can vary from drug to drug and its delivery system. As mentioned previously, patients should be reminded that this medication can take some time to reach a level of maximal benefit, usually on the order of several days. After maximal benefit has been achieved, the drug can be tapered. In some cases, a 14-day course, at the onset of symptoms, is all that is needed to provide relief during an AR episode.<sup>11</sup>

Intranasal corticosteroids have few adverse effects. One randomized, double-blinded, controlled trial looking at pediatric subjects studied mometasone furoate and budesonide versus placebo for a short-term course of 14 days. This study showed no statistically significant difference in lower leg growth rate between groups.<sup>9</sup> Another study looking at intraocular pressures, conducted as a randomized, controlled, double-blinded study comparing placebo, fluticasone propionate, mometasone furoate, and beclomethasone dipropionate for 1 year, showed normal intraocular pressures across all groups.<sup>12</sup> However, in at least one randomized, controlled, double-blinded study, intranasal beclomethasone dipropionate was shown to have a statistically significant decrease in growth-rate for prepubertal children with perennial AR who were followed for 1 year.<sup>13</sup>

## ANTIHISTAMINES

In the 1920s, it was discovered that histamine serves as an important mediator of pathologic allergic disease. Stemming from this basis, antihistamines were some of the first agents geared toward the treatment of atopic conditions (**Table 2**). The first

| <b>Table 2</b><br><b>Antihistamines: generic and brand names</b> |                     |
|------------------------------------------------------------------|---------------------|
| <b>Generic</b>                                                   | <b>Brand</b>        |
| <b><i>First generation</i></b>                                   |                     |
| Azatadine                                                        | Optimine            |
| Azelastine                                                       |                     |
| Brompheniramine                                                  | Dimetane            |
| Chlorpheniramine                                                 | Chlor-Trimeton      |
| Clemastine                                                       | Tavist              |
| Dexchlorpheniramine                                              | Polaramine          |
| Hydroxyzine                                                      | Atarax              |
| Promethazine                                                     | Phenergan           |
| Tripeleennamine                                                  | Pyribenzamine (PBZ) |
| <b><i>Second generation</i></b>                                  |                     |
| Cetirizine                                                       | Zyrtec              |
| Fexofenadine                                                     | Allegra             |
| Loratadine                                                       | Claritin            |
| <b><i>Third generation</i></b>                                   |                     |
| Desloratadine                                                    | Clarinex            |
| Levocetirizine                                                   | Xyzal               |

generation of antihistamines is comprised of six classes of poorly-selective histamine receptor competitive antagonists. These drugs have rapid onset and, although they are quickly efficacious, they wear off rapidly due to their short half-lives. They provide significant relief from AR symptoms such as rhinorrhea. However, this is balanced with a significant side-effect profile. The lack of selectivity for the histamine receptor results in anticholinergic effects due to unintended binding to muscarinic receptors. Consequently, adverse effects include dry mouth, blurred vision, and unwanted mucus thickening. Sedation and cognitive impairment effects stem from central histamine receptor affinity and binding. The first generation antihistamines are lipid soluble and easily cross the blood brain barrier. These medications have limited utility in light of the adverse side effects. This led to the development of second and third generation antihistamines.

Second generation antihistamines were developed in an attempt to improve selectivity and the first group of second generation antihistamines were effective at doing so; however, prolonged Q-T effects were observed in the setting of ingestion of other medications using cytochrome P450 hepatic metabolism. This adverse effect was seen in both terfenadine and astemizole, which led to their removal from the market. The next batch of second generation antihistamines did not have the hepatic side effects of the first group of second generation drugs nor the central histamine-mediated and anticholinergic side effects of first generation medications. Loratadine spearheaded this group of nonsedating H1-blockers. Although not sedating at lower doses, dose-dependent sedation has been observed.<sup>14</sup> Its popularity persists since it was introduced in the early 1990s. Concurrently, the development of fexofenadine followed in the footsteps of terfenadine as a nonsedating second generation antihistamine. It stands unique from loratadine due to its truly nonsedating properties even in the context of increasing dosage. Cetirizine is an active metabolite of hydroxyzine, a first generation antihistamine; therefore, it has slight blood brain barrier penetration

and causes mild drowsiness. Demonstrable efficacy for AR symptoms as well as urticaria supports cetirizine as a useful drug for both respiratory and dermatologic atopic diseases. Loratadine and cetirizine are now available over-the-counter.

The third generation agents are S-isomers of the older antihistamines. Desloratadine and levocetirizine have minimal side effect profiles; however, they offer increased duration of action. Both agents have been shown to have a positive effect of nasal airflow and reduction in nasal congestion. Therefore, they may offer additional benefit to the treatment of AR<sup>15,16</sup> when compared with older antihistamines.

There are two topical intranasal antihistamines available in the United States: azelastine and olopatadine. Azelastine is a second generation antihistamine available for the treatment of seasonal AR. Bitter taste is the most common adverse reaction.<sup>17</sup> Olopatadine not only has antihistaminic properties, but it also possesses mast cell-stabilizing and antiinflammatory properties.<sup>18</sup> It is a new treatment approved by the FDA in 2009 for the management of AR with rapid onset and comparable efficacy to intranasal corticosteroid sprays. It is indicated for seasonal AR in patients aged 6 years or older.<sup>19</sup> Both agents are clinically effective on an as needed and continual basis.<sup>20,21</sup> In a randomized, controlled study looking at children with perennial AR, olopatadine nasal spray twice per day was significantly better than placebo.<sup>22</sup>

### COMBINATION TOPICAL THERAPY

Studies have shown that intranasal corticosteroids when used in combination with oral antihistamines have not resulted in any further benefit for the prophylaxis of seasonal AR.<sup>23</sup> However, there has been new evidence that combination of topical agents, specifically topical corticosteroids and topical antihistamines, provide better symptom relief than either agent alone.<sup>24–26</sup> This efficacy has not been demonstrated in oral antihistamines or leukotriene antagonists when given in combination with an intranasal corticosteroid. There also may be additive benefits for treating patients with moderate-to-severe AR.<sup>18</sup> The safety and adverse effect profiles do not vary from that when these agents are used alone.

### LEUKOTRIENE INHIBITORS

Leukotriene inhibitors target potent inflammatory mediators by competitively blocking the binding of cysteinyl leukotrienes to end-organ receptors. Montelukast is the only leukotriene inhibitor that is FDA-approved for AR, whereas zafirlukast is approved for the management of asthma. Studies have demonstrated clinical efficacy of montelukast for seasonal<sup>27–29</sup> and perennial<sup>30,31</sup> AR. Montelukast significantly reduced exhaled nitric oxide, a marker for airway inflammation, in one study comparing leukotriene inhibitors to other AR agents.<sup>32</sup> Montelukast works primarily through leukotriene receptors C4 and D4, which are found in the upper airways and important in the late-phase response. These agents do not primarily affect sensory nerve fibers, thus, they unlikely have a role in alleviating symptoms of itchiness and sneezing. One meta-analysis of 11 studies concluded that leukotriene receptor antagonists are modestly better than placebo, as effective as antihistamines, but less effective than nasal corticosteroids in improving symptoms and quality of life in patients with seasonal AR.<sup>33</sup> Because montelukast acts throughout the airway, this agent is a reasonable choice for those with concurrent asthma and AR.

Different from montelukast, zileuton acts by blocking the conversion of arachidonic acid into cysteinyl leukotrienes. Zileuton is FDA-approved for use in the treatment of asthma, and has been used in an off-label manner to treat AR and even in the treatment of nasal polyposis.

## MAST CELL STABILIZERS

Cromolyn sodium is a topical over-the-counter nasal agent that works by reducing calcium influx and thereby decreasing the degranulation of histamine from mast cells. However, if the degranulation has already occurred, cromolyn sodium is theoretically not useful. Therefore, it should be used before exposure, which means it would be most useful as a preventative agent. Cromolyn has a very short half-life and therefore can require frequent dosing. The nasal spray can be used for patients aged 2 years and up, 4 to 6 times per day. Cromolyn is indicated in the management of seasonal<sup>34</sup> and perennial<sup>35</sup> AR as well as asthma.

Adverse effects are minimal due to cromolyn's poor systemic absorption. There has been reported sneezing, itching, and unpleasant taste. The safety profile is overall very good for this agent.

## ANTICHOLINERGICS

Ipratropium bromide is an antimuscarinic that can be applied topically to the nasal mucosa, thereby reducing secretory output of the serous and seromucus glands. Its onset of action is relatively quick (within minutes) and, therefore, requires frequent administration throughout the day. Adverse effects include local irritation, dryness, and epistaxis. Systemic absorption is minimal; however, at high doses, systemic anticholinergic side effects can occur.<sup>36</sup> Ipratropium is clinically efficacious against perennial AR in both pediatric<sup>37</sup> and adult<sup>38</sup> populations. Due to the antimuscarinic properties of ipratropium, rhinorrhea is the primary symptom this drug alleviates. Therefore, its use spans all forms of rhinorrhea, including nonallergic forms. However, it has not been shown to be effective against postnasal drip.

## MUCOLYTICS

Thinning out of mucus can be achieved through agents such as guaifenesin. Limited data support its efficacy, in part because clinical trials have not been performed to study its effects on the nasal airway. Lower airway studies have shown some thinning of thickened pulmonary secretions and a role in cough expectorant.<sup>39</sup> It is reasonable to extend these effects to the management of upper airway allergic diseases, especially given that the side effect profile is relatively good. Adverse effects include gastrointestinal upset, dry mouth, rash, and renal stones.

## DECONGESTANTS

Via its effect on alpha-adrenergic receptors, decongestants can increase vasoconstriction and reduce nasal obstruction and congestion. This class of drugs is available over-the-counter in both topical (eg, oxymetazoline) and systemic (eg, phenylephrine, pseudoephedrine) forms.

Oral forms are selective for alpha-2 nasal mucosal receptors. However, they also have nonselective effects on alpha-1 and alpha-2 receptors in the central nervous, cardiovascular, and genitourologic systems. Caution should be exercised in patients with hypertension, cardiac disease, cerebrovascular disease, and urinary retention since these agents can exacerbate symptoms or trigger significant complications. Other adverse effects include insomnia, tremor, restlessness, anxiety, panic attacks, and palpitations. Due to their short half-lives, they come in time-release formulations. When metabolized, pseudoephedrine converts to methamphetamine, which has been used for recreational abuse. Therefore, access to this previously over-the-counter

drug is now more controlled. In addition, this resulted in phenylephrine being used in place of pseudoephedrine in over-the-counter decongestants.

Topical decongestants offer immediate relief from nasal congestion and obstruction. For this reason, these agents can be used on an as needed basis. Adverse reactions include those listed above for systemic agents, although less common due to the relatively small systemic absorption. Prolonged use of these agents can also result in rebound rhinitis, that is, rhinitis medicamentosa. Tolerance of oxymetazoline can develop rapidly resulting in increasing doses and frequencies of application by the patient to achieve the same level of nasal symptom relief. Ultimately, this leads to increased dependence on the medication in the setting of severe nasal congestion. Patients should be advised to use this agent on a daily basis for less than 1 week straight. If rhinitis medicamentosa ultimately does develop, patients can be weaned off the topical decongestant or immediate cessation can also be advocated with the assistance of a short course of concurrent systemic and/or topical corticosteroids.

Monotherapy with decongestants is useful if the only symptom is nasal congestion. However, AR usually presents as a myriad of symptoms. In combination with antihistamines, decongestants can serve as an appropriate complement to medical management of AR. In any setting, caution must be exercised to avoid the major adverse effects of decongestants.

## ANTI-IGE

One of the newer medical approaches to medical treatment of allergic disease is using humanized monoclonal anti-IgE antibodies, for example, omalizumab. This is the first of its class of drugs to be implemented for the management of atopic disease. Specifically, it is FDA-approved for the treatment of severe corticosteroid-dependent asthmatics. It binds to the Fc subunit of the IgE molecule thereby disrupting the binding of antigen to the Fab subunit of the IgE molecule. Thus, there is interference with activation of Th2-mediated cells. Although part of a novel and exciting class of drugs, omalizumab's use in the treatment of AR is currently limited by its cost—approximately \$6,400 to \$32,000 per year per patient. This is difficult for AR patients to afford, especially for a quality-of-life disease. Although, now that it has entered the market for the treatment of severe asthma, the estimated cost is expected to decrease with time.

Clinical studies central on the management of AR are limited for omalizumab.<sup>40</sup> Omalizumab has been shown to be effective for AR in both allergen challenge studies and clinical trials. Multiple randomized, double-blind, placebo-controlled studies have shown efficacy of omalizumab in seasonal<sup>41,42</sup> and perennial<sup>43,44</sup> AR. In addition, a potentially additive benefit from the use of omalizumab is the down-regulation of IgE receptors.<sup>45</sup>

Comparison studies between other treatment options are limited. One randomized controlled trial from Germany<sup>46</sup> examined safety in pediatric subjects with AR by subjecting them to immunotherapy titration phase followed by either placebo or omalizumab. Conclusions from this study supported a good safety profile for children and, although not central to their study objectives, there was data that suggested that AR symptoms were better controlled in the omalizumab arm. Another randomized, controlled study looking specifically at ragweed-sensitive AR subjects treated with either omalizumab or placebo before ragweed season showed lower nasal symptoms scores, rhinitis quality-of-life scores, and days missed from work or school in the omalizumab group. This study also showed dose-dependent reduction of serum IgE levels along with improved subjective complaints.<sup>47</sup> Interestingly, one randomized controlled trial looking at omalizumab versus placebo in the management of recalcitrant chronic rhinosinusitis yielded insignificant outcomes between the two groups.<sup>48</sup>

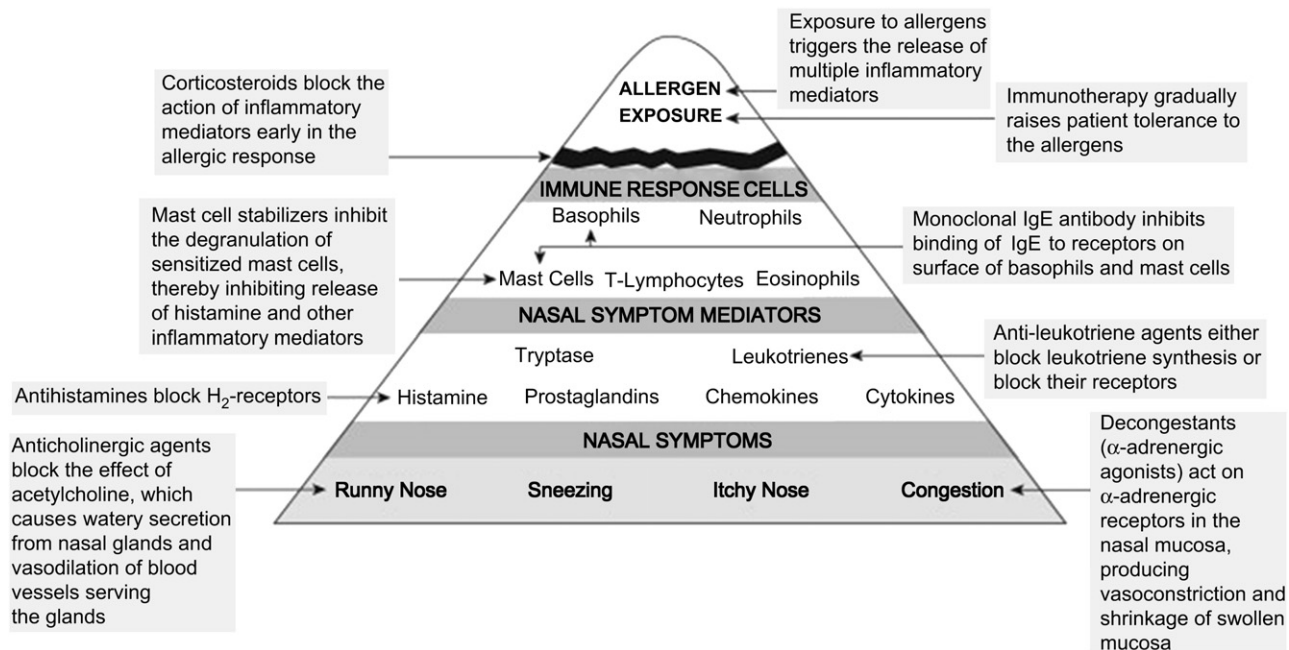


**Fig. 1.** Point-of-action for each drug group. (From Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg* 2007;136(Suppl 6):S107–24; with permission.)

Adverse reactions include malignancies (0.5%), life-threatening anaphylaxis in 1 to 2 of 1000 individuals, urticaria, and serum sickness.<sup>49</sup> Omalizumab has a short half-life, which requires passive high-dose injections every 2 to 4 weeks and therefore frequent office visits.

Research is currently being conducted on the development of active immunization against self-recognizing-IgE.<sup>49</sup> This could potentially reduce the side effect profile and increase the overall safety of anti-IgE therapy.

## MANAGEMENT OPTIONS REVIEW

There are many options to choose from in the management of AR. They act on different points of the early and late phases of allergic reaction (**Fig. 1**). Guidelines have been established to help direct pharmacologic rationale (**Fig. 2**). For mild, intermittent AR, a single-agent of either antihistamine or leukotriene inhibitor usually offers adequate symptom relief without significant adverse reaction risk. The addition of

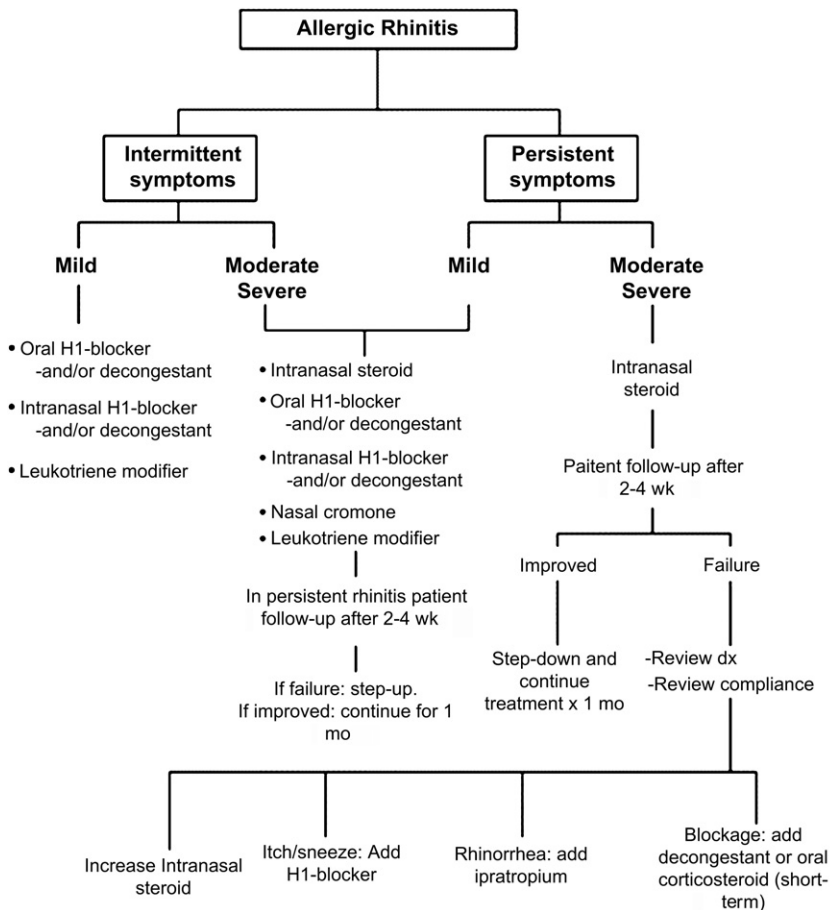


**Fig. 2.** Algorithm for management of AR. (From Greiner AN, Meltzer EO. Pharmacologic rationale for treating allergic and nonallergic rhinitis. *J Allergy Clin Immunol* 2006;118(5): 985–96; with permission.)

a decongestant for nasal congestion or obstruction complaints can also be added to the antihistamine. For moderate-to-severe intermittent or mild persistent AR, the options are greater. Intranasal corticosteroids are the first-line of treatment; however, this regimen can be replaced by antihistamine with or without decongestant, or cromolyn alone. For moderate-severe persistent AR, intranasal corticosteroids are also the first-line treatment. Depending on the follow-up symptoms, the addition of an antihistamine for itchiness or sneezing, ipratropium for rhinorrhea, decongestant for obstruction, or increase in intranasal corticosteroid can be attempted. Some studies are now advocating the use of both topical antihistamines and intranasal corticosteroids, which can be better than each agent alone. Points to consider concerning pharmacotherapy for allergic rhinitis include (1) although avoidance is often the gold standard for management of allergic diseases, it frequently is not practical; (2) AR is a very common quality-of-life disease; (3) management starts with defining the type of allergic rhinitis, intermittent (eg, seasonal) or persistent (eg, perennial); (4) first-line therapy includes intranasal corticosteroids, which have generally shown excellent safety profile and local efficacy; (5) other agents can be used or supplement intranasal corticosteroids depending on symptomatology, such as antihistamines for itching, anticholinergics for rhinorrhea, and decongestants or systemic corticosteroids for nasal obstruction; and (6) monoclonal anti-IgE antibodies comprise a newer class of pharmacotherapeutics, although not yet FDA approved for the treatment of allergic rhinitis, may play a role in future management of AR.

## SUMMARY

AR affects millions of Americans and the numbers continue to increase. Fortunately, there exists a wide array of pharmacotherapeutic options with relatively safe side effect profiles for the management of the varying subtypes of AR. Additionally, there are newer agents on the horizon for the management of AR such as anti-IgE therapy. As future, larger studies are performed, our understanding of the complicated pathophysiology of AR will continually grow and make way for improved medical management of this disease process.

## REFERENCES

1. Reed SD, Lee TA, McCrory DC. The economic burden of allergic rhinitis: a critical evaluation of the literature. *Pharmacoeconomics* 2004;22(6):345–61.
2. Santos CB, Pratt EL, Hanks C, et al. Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol* 2006;97(5):579–86.
3. Blaiss MS. Allergic rhinitis and impairment issues in school children: a consensus report. *Curr Med Res Opin* 2004;20(12):1937–52.
4. Krouse JH, Altman KW. Rhinogenic laryngitis, cough, and the unified airway. *Otolaryngol Clin North Am* 2010;43(1):111–21.
5. Mygind N, Andersson M. Topical glucocorticosteroids in rhinitis. *Acta Otolaryngol* 2006;126:1022–9.
6. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. *Br Med J* 1973;4:464–6.
7. Krouse JH. Allergic rhinitis—current pharmacotherapy. *Otolaryngol Clin North Am* 2008;41(2):347–58.
8. Siegel SC, Katz RM, Rachelefsky GS, et al. Multicentric study of beclomethasone dipropionate nasal aerosol in adults with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1982;69:345–53.

9. Agertoft L, Pedersen S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. *J Allergy Clin Immunol* 1999;104(5):948–52.
10. Cutler DL, Banfield C, Affrime MB, et al. Safety of mometasone furoate nasal spray in children with allergic rhinitis as young as 2 years of age: a randomized controlled trial. *Pediatr Asthma Allergy Immunol* 2006;19(3):146–53.
11. Rinne J, Simola M, Malmberg H, et al. Early treatment of perennial rhinitis with budesonide or cetirizine and its effect on long-term outcome. *J Allergy Clin Immunol* 2002;109:426–32.
12. Bross-Soriano D, Hanenberg-Milner C, Schimelmithz-Idi J, et al. Effects of three nasal topical steroids in the intraocular pressure compartment. *Otolaryngol Head Neck Surg* 2004;130(2):187–91.
13. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. *Pediatrics* 2000;105(2):E23.
14. Simons FE, Simons KJ. Second generation H1-receptor antagonists. *Ann Allergy Asthma Immunol* 1991;66:5–17.
15. Canonica GW, Tarantini F, Compalati E, et al. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy* 2007;62(4):359–66.
16. Bachert C, Bousquet J, Canonica GW, et al. XPERT Study Group. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol* 2004;114(4):838–44.
17. Shah S, Berger W, Lumry W, et al. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. *Allergy Asthma Proc* 2009;30(6):628–33.
18. Kaliner MA, Oppenheimer J, Farrar JR. Comprehensive review of olopatadine: the molecule and its clinical entities. *Allergy Asthma Proc* 2010;31(2):112–9.
19. Roland PS, Ryan MW, Wall GM. Olopatadine nasal spray for the treatment of seasonal allergic rhinitis in patients aged 6 years and older. *Expert Opin Pharmacother* 2010;11(9):1559–67.
20. Roland PS, Marple BF, Wall GM. Olopatadine nasal spray for the treatment of allergic rhinitis. *Expert Rev Clin Immunol* 2010;6(2):197–204.
21. Kaliner MA. Azelastine and olopatadine in the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol* 2009;103(5):373–80.
22. Okubo K, Okuda M, Magara H, et al. Olopatadine hydrochloride in children: efficacy and safety for perennial allergic rhinitis. *Curr Med Res Opin* 2010;26(7):1657–65.
23. Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. *Drug Invest* 1994;8:225–33.
24. Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol* 2010;105(2):168–73.
25. LaForce CF, Carr W, Tilles SA, et al. Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis. *Allergy Asthma Proc* 2010;31(2):132–40.
26. Bernstein JA. Azelastine hydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Curr Med Res Opin* 2007;23(10):2441–52.
27. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;32:1020–8.

28. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003;58:1268–76.
29. Chervinsky P, Philip G, Malice MP, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol* 2004;92:367–73.
30. Chen ST, Lu KH, Sun HL, et al. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2–6 yr. *Pediatr Allergy Immunol* 2006;17:49–54.
31. Patel P, Philip G, Yang W, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005;95:551–7.
32. Hung CH, Hua YM, Hsu WT, et al. Montelukast decreased exhaled nitric oxide in children with perennial allergic rhinitis. *Pediatr Int* 2007;49(3):322–7.
33. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116(5):338–44.
34. Meltzer EO, NasalCrom Study Group. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther* 2002;24:942–52.
35. Cohan RH, Bloom FL, Rhoades RB, et al. Treatment of perennial allergic rhinitis with cromolyn sodium. Double-blind study on 34 adult patients. *J Allergy Clin Immunol* 1976;58:121–8.
36. Wood CC, Fireman P, Grossman J, et al. Product characteristics and pharmacokinetics of intranasal ipratropium bromide. *J Allergy Clin Immunol* 1995;95:1111–6.
37. Kim KT, Kerwin E, Landwehr L, et al. Use of 0.06% ipratropium bromide nasal spray in children aged 2 to 5 years with rhinorrhea due to a common cold or allergies. *Ann Allergy Asthma Immunol* 2005;94:73–9.
38. Kaiser HB, Findlay SR, Georgitis JW, et al. Long-term treatment of perennial allergic rhinitis with ipratropium bromide nasal spray 0.06%. *J Allergy Clin Immunol* 1995;95:1128–32.
39. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2008; 1:CD001831.
40. Morjaria JB, Polosa R. Off-label use of omalizumab in non-asthma conditions: new opportunities. *Expert Rev Respir Med* 2009;3(3):299–308.
41. Casale TB. Anti-IgE (Omalizumab) therapy in seasonal allergic rhinitis. *Am J Respir Crit Care Med* 2001;164(Suppl):S18–21.
42. Adelroth E, Rak S, Huuhtela T, et al. Recombinant humanized mAb-E25, an anti IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;106:253–9.
43. Chervinsky P, Casale T, Townley R, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2003;91:160–7.
44. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004;59:709–17.
45. Storms W. Allergens in the pathogenesis of asthma: potential role of anti-immunoglobulin E therapy. *Am J Respir Med* 2002;1(5):361–8.
46. Kamin W, Kopp MV, Erdnuess F, et al. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010;21(1 Pt 2):e160–5.

47. Stokes J, Casale T. Anti-IgE therapy. In: Atkinson NF, Bochner BS, Busse WW, et al, editors. Middleton's allergy: principles and practice. 7th edition. St Louis (MO): Mosby; 2008. p. 1679–89.
48. Pinto JM, Mehta N, DiTineo M, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 2010;48(3):318–24.
49. Peng Z. Vaccines targeting IgE in the treatment of asthma and allergy. *Hum Vaccin* 2009;5(5):302–9.