Background:
The National Pharmacy & Therapeutics Committee (NPTC) reviewed allergic rhinitis (AR) and available treatment options at the August 2018 meeting. Prior to the review, the National Core Formulary (NCF) included any 2nd generation, long-acting H1 Antagonist; any intranasal corticosteroid; and montelukast. After a comprehensive review of the aggregate clinical data addressing the efficacy, safety, and tolerability of available pharmacologic treatment options, the NPTC made no changes to the NCF.

Allergic rhinitis is an immunoglobulin (IgE)-mediated inflammatory nasal condition triggered by allergens and characterized by symptoms of sneezing, nasal obstruction, and mucus discharge. The estimated lifetime prevalence of AR in the U.S. is between 11-33%. AR has a significant impact on patients’ quality of life, including productivity, activity levels, emotional and social well-being, and memory function. AR is the most common chronic condition in children, and can affect learning and development. Overall, AR causes an estimated 3.5 million lost workdays and 2 million lost school days per year in the U.S., with an overall financial cost of $2-5 billion per year.

Discussion:
AR can be classified on the pattern of symptoms, severity, and potential triggers. Seasonal allergic rhinitis (SAR) refers to disease triggered by seasonal allergens such as pollens or grasses, which vary depending on location and climate. Perennial allergic rhinitis (PAR) is characterized by symptoms that occur in response to year-round environmental allergens such as dust mites, mold, animals, or occupational allergens. Alternatively, AR can be classified as intermittent, persistent, or episodic. Clinical guidelines and strategies are dependent on the pattern of symptoms and triggers, and may include pharmaceutical treatment, allergen avoidance, surgery immunomodulatory therapy, and adjunct therapies such as intranasal saline. Pharmacotherapy remains the primary treatment modality for the majority of allergy sufferers. Studies of patient preferences show that allergy sufferers value treatments that are effective until the time of next dose, allows them to wake up with symptoms under control, provides 24-hour relief, provides relief within an hour, and does not cause excessive drowsiness.

Pharmaceutical options for AR are aimed at blocking or ameliorating the effects of the IgE-mediated inflammatory process. Drug classes included in the NPTC discussion were the 2nd generation oral H1 antihistamines, intranasal corticosteroids, intranasal antihistamines, combination intranasal corticosteroid and antihistamines, mast cell stabilizers, and leukotriene inhibitors. Brief discussion of adjunct therapies such as decongestants and intranasal saline was included for completeness.

The 2018 International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis is a comprehensive review of the state of AR. The findings of the consensus statement regarding pharmacological management of AR can be summarized below. The preponderance of evidence examining oral H1 antihistamines, intranasal corticosteroids, intranasal antihistamines, combined intranasal corticosteroids and antihistamines, and leukotriene antagonists is of high quality.

Oral H1 antihistamines have consistently shown efficacy in reducing the cardinal symptoms of AR, including nasal itching, sneezing, rhinorrhea and nasal obstruction. Mild side effects such as drowsiness, headache, nausea and dry mouth are minimal in the 2nd generation H1 antihistamines, and direct costs of the medications are low. Newer generation antihistamines are strongly recommended for the 1st line treatment of AR, while 1st generation antihistamines with a more severe side effect profile were not recommended for routine use.

Intranasal corticosteroids (INCS) are effective in reducing both the nasal and ocular symptoms of AR, and the preponderance of evidence indicates superiority in efficacy to oral antihistamines and leukotriene antagonists (LTRAs). Local adverse effects such as epistaxis do occur with increased frequency compared to placebo in prolonged administration studies, and early INCS with increased systemic
absorption may have some negative effects on short-term growth in children, although it is unclear whether these effects translate into long-term growth suppression\(^9\).

Intranasal antihistamines are also recommended as a potential 1\(^{\text{st}}\) or 2\(^{\text{nd}}\) line treatment for AR. They provide more effective relief of nasal congestion than oral antihistamines, are generally more effective than INCS for ocular symptoms, and show consistent reduction in AR symptoms and improvement in quality of life (QOL). However, they have an unpleasant taste and are less effective in reducing nasal congestion than INCS\(^9\).

Combination intranasal antihistamine and INCS show promise in the treatment of AR. Combination intranasal treatment has rapid onset and is consistently shown to be more effective than either INCS or antihistamine alone. However, unpleasant taste may limit its use and is generally cost prohibitive compared to other effective pharmaceutical options. It is recommended as a 2\(^{\text{nd}}\) line therapy for the treatment of AR when monotherapy fails\(^9\).

Leukotriene antagonists show effective reduction in symptoms and QOL improvement compared to placebo, but are consistently inferior to INCS. They are equivalent or inferior to oral antihistamines, but are not as cost effective. Overall, there is insufficient evidence to recommend LTRA’s monotherapy but they may be considered as 2\(^{\text{nd}}\) line therapy, particularly in patients with comorbid AR and asthma\(^9\).

Cromolyn, an intranasal mast cell stabilizer, is effective in reducing sneezing, rhinorrhea and nasal congestion compared to placebo. Rare local side effects include nasopharyngeal irritation, sneezing, rhinorrhea, and headache. They are cost effective and can be useful for preventative, short-term use. However, their use in long-term management is limited by the necessity for 3-6 times daily dosing, which makes it impractical for consistent use\(^9\).

Oral decongestants (specifically pseudoephedrine), intranasal decongestants, and intranasal anticholinergics were recommended as potential options for adjunctive therapy in a limited, short-term setting. Intranasal decongestants, in particular, present a high risk of rhinitis medicamentosa. Pseudoephedrine also must be used with caution due to cardiovascular risks and risk of diversion. Nasal saline, on the other hand, is strongly recommended as adjunct therapy with strong evidence for efficacy and tolerability\(^9\).

The following clinical treatment guidelines for AR were also included in the NPTC discussion.

The MACVIA treatment algorithm recommends “any” 1\(^{\text{st}}\) line treatment for mild or intermittent symptoms of AR, including oral or intranasal antihistamines, INCS, or a combination intranasal antihistamine/INCS (based on patient preference, price, and availability). For more severe symptoms that are also persistent, the recommendation is to use either an INCS or a combination intranasal antihistamine/INCS\(^11\).

The Pharmacologic Treatment of Seasonal Allergic Rhinitis: Synopsis of Guidance From the 2017 Joint Task Force on Practice strongly recommends monotherapy with an INCS rather than combination of an INCS with an oral antihistamine in patients >12 years and strongly recommends an INCS over a LTRA. The synopsis also included a weak recommendation for the combination of an INCS and intranasal antihistamine for initial treatment\(^12\).

The Clinical Practice Guideline: Allergic Rhinitis 2015 American Academy of Otolaryngology included six action statements related to pharmacotherapy. These include recommending INCS for patients with a clinical diagnosis of AR whose symptoms affect their QOL (strong recommendation); that clinicians should recommend oral 2\(^{\text{nd}}\)-generation/less sedating antihistamines for patients with AR and primary complaints of sneezing and itching (strong recommendation); an option for clinicians to offer intranasal antihistamines for patients with seasonal, perennial, or episodic AR; a recommendation for clinicians not to offer LTRA’s as primary therapy for AR patients; and an option for clinicians to offer combination pharmacologic therapy in AR patients who have inadequate response to pharmacologic monotherapy\(^8\).

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision recommends INCS for SAR and PAR, with or without the addition of intranasal or oral antihistamines. The guidelines also include a recommendation for either oral antihistamines or LTRA for SAR, but recommend oral antihistamines over LTRA for PAR. The guidelines make a conditional recommendation for INCS over
intranasal antihistamines as monotherapy, and conditionally recommend either intranasal antihistamines or oral antihistamines for the treatment of SAR and PAR\textsuperscript{13}.

**Findings:**

The clinical literature strongly support INCS as the preferred primary monotherapy for AR, with the option for oral antihistamines or intranasal antihistamines as reasonable alternatives, based on patient preference. Combination INCS and intranasal antihistamines are potential 2\textsuperscript{nd} line therapies but are generally cost prohibitive. LTRA’s may also be considered as 2\textsuperscript{nd} line or adjunctive therapy, particularly in patients with comorbid asthma. In consideration of these findings, the NPTC consensus was that the existing formulary options of an INCS, 2\textsuperscript{nd} generation, long-acting oral antihistamine, and LTRA provide a sufficient range of treatment options. Due to unfavorable comparison with INCS in terms of efficacy\textsuperscript{9}, and unfavorable comparison with oral antihistamines due to palatability\textsuperscript{10}, the NPTC decided against the addition of intranasal antihistamines.

The NPTC considered evidence presented in a drug class review of “newer” antihistamines that evaluated 58 high quality studies, meta-analyses, and systematic reviews. The evidence suggested that sedation was rare, but was somewhat more common with cetirizine and levocetirizine than with loratadine or desloratadine. Headache reported were similar with cetirizine, loratadine, and fexofenadine\textsuperscript{14}. Head-to-head comparisons of efficacy of 2\textsuperscript{nd} generation antihistamines showed no significant or reproducible difference between loratadine, desloratadine, cetirizine, levocetirizine, and fexofenadine in adults. In children, one fair quality study suggested that cetirizine may be slightly more efficacious in PAR, but there were no head-to-head studies comparing different oral antihistamines in SAR\textsuperscript{14}. Overall, the NPTC did not feel that the evidence was compelling to recommend a specific oral 2\textsuperscript{nd} generation antihistamine.

Review of studies comparing the efficacy of available INCS also failed to demonstrate convincing evidence to support one steroid spray over another in the treatment of SAR or PAR\textsuperscript{15}. All sprays have a similar side-effect profile. The rate of epistaxis was noted to be 17-23% among all formulations (notably, the rate of epistaxis in placebo groups was 10-15%)\textsuperscript{16}. In considering safety, budesonide is the only INCS classified as pregnancy category B. However, the newer formulations of INCS, including ciclosporine, fluticasone furoate, fluticasone propionate, and mometasone are all <1% bioavailable, and studies evaluating effects on growth and bone density in pediatric patients with these agents show convincing evidence of their safety\textsuperscript{17}. Limitations for use of INCS include patient distaste (especially formulations that contain alcohol and fragrance) and concerns over the drug losing effect over time. In order to ensure appropriate patient utilization of INCS, education on use and minimizing/mitigating side effects is essential\textsuperscript{16}. As with the oral antihistamines, the NPTC felt that these considerations are best decided at the service unit level, and declined to name a specific INCS.

**Conclusions:**

In conclusion, the NPTC found that the existing formulary options provide adequate treatment avenues for the management of allergic rhinitis. Due to its role as adjunctive and 2\textsuperscript{nd} line therapy in patients with comorbid allergic rhinitis and asthma, the NPTC retained montelukast on the NCF.

**References:**