

# Early and late phase allergic rhinitis – pathogenesis and treatment options

S Davis

Amayeza Information Services

Corresponding author, email: sumari@amayeza-info.co.za

## Abstract

Allergic rhinitis is an inflammatory condition affecting the nasal mucosa. It presents as nasal itching, sneezing and rhinorrhoea during the early phase. This is often followed by a secondary inflammatory response that occurs 6–12 hours later resulting in nasal congestion. This article discusses the early and late phase pathogenesis of allergic rhinitis, treatment options, and recommendations for a stepwise treatment plan.

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## Introduction

Allergic rhinitis (AR) affects up to 40% of the world population and is associated with symptoms consisting of sneezing, rhinorrhoea, nasal congestion and itching of the nose, eyes, ears, and palate.<sup>1-3</sup> An initial response occurs within seconds or minutes of exposure to an allergen and this early response peaks within 15–30 minutes. Approximately 50% of patients experience a second nasal allergic reaction that peaks at 6–12 hours following exposure and this late phase response is thought to be important in establishing the chronicity of the disorder.<sup>2</sup>

## Mechanisms of upper airway allergic reactions simplified

Allergic rhinitis only occurs in patients with a genetic predisposition to developing allergies. Although all people are constantly exposed to environmental allergens, only those born with the ability to become sensitised, develop symptoms.<sup>3</sup> Antigen-producing cells in the mucosa process allergens to sensitise mast cells and basophils in the immune system.<sup>4</sup> Repeated exposure to the same allergen results in production of IgE antibodies that bind to the sensitised surfaces of mast cells and basophils to release a number of mediators.<sup>3,5</sup> The allergic response then develops in two different patterns according to time sequence.<sup>4</sup>

### Early phase pathogenesis

Within seconds to minutes of exposure to an allergen, an immediate allergic response is observed, which peaks in 15–30 minutes.<sup>2</sup> Secretion of mediators such as histamine, prostaglandins, leukotrienes and other components from mast cells results in activation of H<sub>1</sub> receptors on sensory nerves and mucous glands with increased watery mucous production.<sup>1,3</sup> These are associated with symptoms such as sneezing and rhinorrhoea respectively.<sup>1,4</sup> Histamine also causes increased vascular permeability and vasodilatation that leads to engorgement of blood vessels in the nasal mucosa and the sensation of nasal congestion.<sup>1</sup> After about 30 minutes, prostaglandin and histamine levels return to normal.<sup>2</sup>

### Late phase pathogenesis

In contrast to the early phase, eosinophil chemotaxis is the main response in the second phase allergic response, that occurs 6–12 hours after initial exposure.<sup>4</sup> This involves the influx of migratory immune cells and subsequent release of additional cytokines and mediators such as leukotrienes, prostaglandins and platelet activating factor (PAF).<sup>1</sup> These inflammatory cells break up and remodel normal nasal tissue.<sup>4</sup> Whilst rhinorrhoea and sneezing persist, these processes are responsible for symptoms of nasal congestion typical of the second phase reaction.<sup>1</sup> This secondary inflammatory response is thought to be important in establishing chronicity of the disorder.<sup>2</sup>

### Symptoms

Symptoms associated with the early phase response in allergic rhinitis include sneezing, nasal itching and rhinorrhoea.<sup>5</sup> Patients often also present with ocular itching, redness and tearing during the first phase response. The late phase reaction is associated with tissue remodelling, tissue oedema and continued nasal congestion. These late phase reactions also contribute towards bronchial hyper-responsiveness.<sup>7</sup> Nasal congestion is associated with sleep-disordered breathing that can lead to fatigue, depressed mood and compromised cognitive function.<sup>6</sup> Many of the mediators of AR responses such as histamine, leukotrienes, cytokines and prostaglandins also play a direct role in sleep regulation and might be directly involved in sleep disorders, independent of nasal obstruction.<sup>7</sup>

### Pharmaceutical management

Since there is no cure for AR and complete avoidance of known allergens is not always possible, the aim is to manage and achieve control of symptoms with the available therapeutic options.<sup>1</sup> Combination therapies should, in theory, cover a broader range of inflammatory pathways and symptoms.<sup>1</sup>

### Intranasal corticosteroids

Intranasal steroids (INS) are the mainstay of treatment for AR<sup>3</sup> and are potent inhibitors of the late-phase allergic reaction.<sup>7</sup> INS

are particularly useful for improving nasal congestion.<sup>3</sup> INS have broad anti-inflammatory actions and reduce mucosal oedema and vascular leakage to improve symptoms of rhinorrhoea and nasal congestion. In addition, they also reduce the number of histamine-containing mast cells and the release of mediators to reduce sneezing and itching.<sup>3,6</sup> Therapeutic effects of INS are seen within seven hours of administration and the number of eosinophils and basophils are reduced within one week.<sup>4</sup> Maximum effects are seen two weeks after start of treatment and patients should therefore be informed of the importance of continued compliance with prophylactic INS to obtain optimal efficacy.<sup>3,4</sup>

Although the clinical effects of different INS preparations are similar, they differ in terms of systemic absorption. For mometasone furoate and fluticasone propionate, systemic absorption is very low ( $\leq 0.1\%$  and  $\leq 2\%$ , respectively). Systemic absorption of triamcinolone acetonide and beclomethasone dipropionate are 46% and 34% respectively.<sup>8</sup> INS with higher systemic absorption rates are associated with a higher incidence of systemic side-effects.

### Antihistamines

The second-generation oral antihistamines are most beneficial in reducing nasal itching, sneezing, rhinorrhoea as well as ocular symptoms following histamine release.<sup>3</sup> They have a limited effect on reducing congestion but cause less sedation than the first-generation antihistamines.<sup>3</sup> Rupatadine is a long-acting oral  $H_1$ -antihistamine that, in addition to being a selective  $H_1$ -antagonist, also acts as a potent antagonist at PAF receptors, responsible for vasodilatation and vascular permeability that leads to rhinorrhoea and nasal congestion.<sup>9-11</sup> Rupatadine is beneficial in that it reduces symptoms in both the early and late phase of allergic rhinitis.<sup>12</sup>

Intranasal application of antihistamines (e.g. azelastine or levocabastine) facilitates higher concentrations of drugs directly to the nasal mucosa, thus enhancing the local anti-allergic and anti-inflammatory effects with a reduced risk of side-effects when compared to systemic therapy.<sup>1,7</sup> Intranasal azelastine applied twice daily was shown to reduce symptoms in patients who do not respond to oral antihistamines.<sup>4</sup> However, they are less effective than INS and ineffective in reducing ocular symptoms. Some side-effects of intranasal antihistamines include metallic taste and mild sedation.<sup>4</sup>

### Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) such as montelukast block the activity or secretion of leukotrienes, potent inflammatory mediators associated with nasal congestion, mucus production and inflammatory cell recruitment.<sup>7</sup> Montelukast is effective in reducing nasal and ocular symptoms and improves nasal obstruction. The effects in treating allergic rhinitis symptoms are estimated to be similar to those of antihistamines but less than those of INS.<sup>4</sup>

### Decongestants

Decongestants such as phenylephrine cause vasoconstriction of the superficial blood vessels in the nasal mucosa to reduce swelling of the mucosal tissue. They reduce vascular leakage which lessens rhinorrhoea and helps decrease nasal congestion.<sup>3</sup> Decongestants can cause significant side-effects such as hypertension, insomnia, irritability, and loss of appetite. Although

intranasal decongestants such as phenylephrine, oxymetazoline or xylometazoline can provide rapid temporary relief, they can cause rebound congestion, especially with prolonged use, and can also result in the same systemic side-effects as seen with oral decongestants.<sup>3</sup>

### A stepwise approach in managing AR

The general approach to managing AR is to avoid or reduce exposure to known allergens as far as possible. Help patients identify their risk factors and time periods to ensure maximum therapy during these time frames.<sup>3</sup>

Almost all patients benefit from INS and the dosing frequency will depend on the severity of the symptoms. Antihistamines can be added either as part of the daily regimen or on an as-needed basis. Decongestants may be added for short periods of time in patients, only when their symptoms of congestion are not adequately controlled with INS and antihistamine treatment. LTRAs may have added benefit and are usually considered in patients with concomitant asthma.<sup>3</sup>

### Conclusion

Allergic rhinitis presents with early symptoms of sneezing, nasal itching and rhinorrhoea within seconds or minutes of exposure to an allergen and up to 50% of patients continue to develop a secondary inflammatory response around 6–12 hours later that worsens initial symptoms of nasal congestion. A stepwise approach is recommended when managing AR. INS have a wide range of anti-inflammatory effects and remain the mainstay of treatment with optimal effects seen after two weeks of consistent use. Antihistamines may be used as part of the daily regimen or on an as-needed basis with intranasal application resulting in higher concentration at the nasal mucosa and less systemic side-effects. Rupatadine is an antihistamine with a dual mechanism of action and effectively manages symptoms in both the early and late phase of AR.

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