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Summary:

Rhinitis is a heterogeneous condition that has been associated with inflammatory responses as in allergic rhinitis but can also occur in the absence of inflammation such as in so-called 'idiopathic' (previously 'vasomotor') rhinitis. Allergic rhinitis affects approximately 1 in 4 of the population of westernised countries and is characterized by typical symptoms of nasal itching, sneezing, watery discharge and congestion. The intention of this review is to illustrate key concepts of the pathogenesis of rhinitis. Imbalance in innate and adaptive immunity together with environmental factors is likely to play major roles. In allergic rhinitis, initial allergen exposure and sensitization involves antigen presenting cells, T and B lymphocytes and results in the generation of allergen-specific T cells and allergen specific IgE antibodies. On re-exposure to relevant allergens crosslinking of IgE on mast cells results in the release of mediators of hypersensitivity such as histamine and immediate nasal symptoms. Within hours, there is an infiltration by inflammatory cells, particularly Th2 T lymphocytes, eosinophils and basophils into nasal mucosal tissue that results in the late-phase allergic response. Evidence for nasal priming and whether or not remodelling may be a feature of allergic rhinitis will be reviewed. The occurrence of so-called 'local' allergic rhinitis in the absence of systemic IgE will be discussed. Non-allergic (non-IgE mediated) rhinitis will be considered in the context of inflammatory and non-inflammatory disorders.

Key words: Allergic rhinitis, non-allergic rhinitis, pathogenesis, priming, remodelling,

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Introduction:

Rhinitis is a common heterogeneous chronic disorder in both children and adults that is defined as an inflammation of the nasal mucosa and characterised by the presence of one or more nasal symptoms that includes sneezing, itching, nasal discharge and nasal blockage. Allergic rhinitis is the most common form of non-infectious rhinitis that is associated with an IgE-mediated immune response against environmental allergens [1]. There are a number of rhinitis phenotypes that may be classified as shown in Table 1.

The International Study of Asthma and Allergies in Childhood (ISAAC) revealed an increased worldwide trend of rhinitis with an average prevalence of 8-15% in children [2, 3], with a prevalence in the general population ranging from 10-40% in industrialised countries [4-7]. Studies of the natural history of rhinitis in children have shown a prevalence of 2.8% and 11.8% at 4 years and 18 years of age for non-allergic rhinitis and, respectively, 3.4% and 27.3% for allergic rhinitis. The adjusted prevalence rate in adults was found to be 9.6% for non-allergic rhinitis and 29.8% for allergic rhinitis. Children with a parental family history of atopic diseases develop symptoms more frequently and at a younger age than those with non-allergic parents. There is a male predominance of allergic rhinitis and female predominance of non-allergic rhinitis during adolescence and in adulthood [5, 8-10]. There is high risk of developing asthma in both children and adults with allergic rhinitis [11, 12].

Allergic rhinitis can be seasonal or perennial based on temporal patterns of symptoms and relevant allergens. The distinction between seasonal and perennial is not globally applicable, hence, the international working group Allergic Rhinitis and its Impact on Asthma (ARIA) has revised the guidelines of allergic rhinitis on the basis of the severity (mild, moderate and severe) and duration (intermittent, persistent) of symptoms [1]. Both approaches are useful and not mutually exclusive. The ARIA approach is particularly applicable in countries where

pollinosis occurs all year round with no defined season or a very prolonged season. The seasonal/perennial approach is more relevant in countries where there are clear cut seasonal allergen exposures.

Pathogenesis of Rhinitis:

The nasal cavity is divided by the nasal septum, which is composed of bone and cartilage. The superior, middle and inferior turbinates are located laterally and lined with pseudostratified columnar respiratory epithelium. The nasal mucosa acts as an air conditioner that regulates inhaled air temperature, humidification and cleans the inspired air. The healthy nasal airway epithelium comprises of ciliated cells, mucus-secreting goblet cells and basal cells which represent 50-90% of airway epithelial cell population. The epithelium rests on a basement membrane zone and covers submucosal structures thereby forming the link between environmental exposure and the host immune system [13,14]. The nasal submucosa comprises serous, mucous and seromucous glands, extensive vascular and neural networks and cellular and extracellular matrix components.

Nasal mucus acts as a barrier against external pathogens and has antioxidant, antiprotease, and antimicrobial properties. Major constituents of nasal mucus are the mucins which play an important role in antimicrobial and anti-inflammatory defences, as well as in mucociliary clearance [15, 16]. Ciliated epithelium traps foreign bodies in a thin layer of surface mucus that migrates towards the posterior nasopharynx. During inflammation mucociliary clearance may be impaired leading to exuberant and excessive collection of mucus manifest as increased anterior and/or posterior nasal discharge. Nasal vascularity provides an optimal homeostatic function while inflammation leads to increased vascular permeability and engorgement causing significant nasal congestion. Parasympathetic cholinergic nerve stimulation results in mucus production from nasal airway glands which also lead to nasal

discharge and congestion. Sympathetic fibres, which mainly follow the blood vessels, release noradrenaline and neuropeptides which induce vasoconstriction and increased nasal patency. Sympathetic tone fluctuates throughout the day resulting in increasing/decreasing nasal airway resistance in alternate nostrils every 2-4 hours – the phenomenon known as the 'nasal cycle' [17, 18].

Allergic rhinitis

Allergic rhinitis is an IgE-mediated disease which is predominantly caused by environmental allergen exposure in genetically predisposed individuals, and is partly due to alterations in their immune system. Common allergens implicated in allergic rhinitis are mainly proteins and glycoproteins found in airborne particles. Important allergens causing intermittent or persistent symptoms vary in different parts of the world. In UK grass pollinosis is the most common, in North America ragweed and Mediterranean areas Parietaria predominates. Dust mite faecal particles, cockroach residues and animal danders are common perennial allergens that may provoke intermittent or persistent symptoms all year round in temperate climates. Following inhalation, allergen particles are deposited on the surface of the nasal epithelium with subsequent elution of soluble allergenic proteins and their diffusion into the nasal mucosa.

During the initial sensitization process in allergic rhinitis, several common aero-allergens facilitate allergen access to antigen presenting cells through their protease activities which cleave tight junctions in the airway epithelium and activate epithelial cells. Evidence extrapolated from studies of the bronchial epithelium in asthma suggest that activated/damaged nasal epithelial cells secrete thymic stromal lymphopoietin (TSLP), IL33, IL-25 and other cytokines and chemokines that affect group 2 innate lymphoid cells (ILC2s) and Th2 T lymphocytes directly or via interaction with antigen presenting cells located

within and below the nasal epithelium [19-21] (Figure 1). In addition these epithelial cytokines have recently been shown to be important for the activation of ILC2s that lack T cell receptors and do not express T cell nor other cell lineage markers [22]. ILC2 cells express CRTh2, CD127 (the interleukin 7 receptor) and ST-2, the receptor for IL-33. They preferentially express Th2 cytokines, particularly IL-5 and IL-13 and have the potential to augment local Th2-driven allergic inflammation. Antigen presenting cells that include immature dendritic cells (expressing CD1a, CD11c) and macrophages capture allergens, mature and migrate to the draining lymph nodes, where they present processed allergen to naive T cells that are subsequently skewed in favour of Th2 T-cell development [23-25]. Recently it has been shown that ILC2s may also modulate and polarize naïve T cells into Th2 cells by producing IL-13 which is necessary for dendritic cells to be trafficked into lymph nodes and subsequently leads to Th2 cell priming [26,27]. T cells activated during allergic inflammation proliferate into effector memory allergen-specific Th2 cells that release IL-4, IL-5, IL-9 and IL-13. Antigen presenting cells may also be conditioned by Th2–inducing cytokines such as TSLP to 'preferentially' polarize naive T cells towards Th2 effector phenotypes [28]. Allergen-activated Th2 cells secrete IL-4 that maintains the Th2-cell lineage and recruits more T helper cells into this lineage. Th2 cells also secrete IL-13 and express CD40 ligand (CD40L), which together with IL-4 promotes heavy-chain class switching in B lymphocytes in favour of IgE production. IgE antibodies bind to the high-affinity receptor (FcεRI) on the surface of mast cells, basophils and antigen-presenting cells (APCs) and sensitize these cells to allergens [29]. On allergen re-exposure, cross-linking of IgE–FcεRI complexes on APCs, facilitates allergen uptake by APCs for processing and presentation, while IgE–FceRI interaction on mast cells and basophils with allergen induces the classic early phase allergic reaction (EPR). A proportion of subjects subsequently develop a late phase inflammatory response (LPR) (Figure 1).

Allergic rhinitis is an excellent model for studying allergic inflammation, where the triggering factors can clearly be identified, particularly in subjects with seasonal rhinitis who can be monitored in and out of the pollen season. Nasal secretions and mucosal tissue are easily accessible for invasive and non-invasive procedures such as biopsies and collection of nasal secretions for analysing clinical and immunological responses in allergic rhinitis [30-32]. Furthermore, nasal allergen challenge represents an *in vivo* experimental model that has contributed immensely to understanding the underlying mechanisms of allergic rhinitis [33-35].

Nasal allergen challenge results in tissue eosinophilia and an increase in cells expressing Th2 cytokines [36]. More recently nasal allergen challenge has been shown to result in an increase in T cells that express the prototypic Th2 chemokine receptor CCR4 [37] and increased numbers of the Th2 transcriptional factors $STAT6^{+}$ and $GATA3^{+}$ in T cells and an increase in the ratio of $GATA3^{+}$:T-bet^{+} T cells in the nasal mucosa compared to healthy individuals [38]. This supports the hypothesis that dysregulation of Th1 transcription factors may at least in part be responsible for the exaggerated Th2 responses observed in allergic rhinitis.

Regulatory T cells (T regs) represent a distinct subtype of T cells that down-regulate effector T cell responses. They are characterized by the expression of CD25 on their surface and signal through the transcriptional factor forkhead box p3 (FOXP3), and secrete suppressive cytokines such as IL-10 and TGF-beta that cross-talk with dendritic cells to induce tolerance [39,40]. Regulatory T cells directly suppress effector T cells by a number of mechanisms that include the release of soluble cytokines and via cell-cell contact. They also compete with naive T cells in a physical manner by creating aggregates around DCs *in vitro* and inhibiting their maturation [41]. It has been demonstrated that there is a fine balance of immune response between allergic and healthy controls in that, allergen specific IL-4 secreting Th2 cells predominate mainly in sensitized individuals while T-regs predominate in healthy

controls [42,43]. This was further demonstrated recently in an *in vivo* human allergen challenge model that revealed a significant increase in dendritic cells that expressed TSLP receptors [19] and a substantial reduction in DC expressing IL-10 in local nasal mucosa of allergic rhinitis individuals compared to healthy controls [44]. These data suggest that T regs may be defective in their ability to suppress type 2 inflammatory responses in allergic individuals.

Early phase allergic response (EPR)

Allergen challenge in IgE-sensitised individuals results within minutes in early phase symptoms such as sneezing and itching followed by rhinorrhoea and nasal blockage which then tend to resolve within 1 hour. This response stems from allergen crosslinking complexes of sensitized IgE with FcεRI at the surface of mast cells and basophils leading to degranulation and the release of preformed mediators such as histamine and tryptase, and the *de novo* generation of mediators from the membrane lipid such as cysteinyl leukotrienes (leukotrienes C_4, D_4 and E_4) and prostaglandins D_2 [35,45] (Figure 2). Histamine elicits itching through H_1-receptors that acts on sensory nerves endings, leading to a systemic reflex, such as a paroxysm of sneezing. Leukotrienes, prostaglandin D_2, and vascular endothelial growth factors (VEGF) cause plasma leakage from blood vessels leading to oedema, pooling of blood in the capacious venous sinusoids and an increase in glandular mucus secretion, all of which may contribute to sensation of nasal congestion [46,47].

Human nasal provocation studies with cat and grass allergens have examined the kinetics of local and systemic responses to mucosal allergen exposure [31,33,48-50]. It has been demonstrated that nasal fluid tryptase and histamine levels peak at 5 minutes indicating immediate activation of local mast cells after allergen exposure followed by subsequent

increases in the expression of surface activation markers such as CD63 on circulating basophils.

Murine experimental model of allergic rhinitis have been recently developed to trigger nasal responses without lower airway involvement [51]. These models have recently highlighted the essential role of mast cells and basophils in eliciting sequential or biphasic cascades of events in allergic rhinitis. After activation of tissue mast cells through FcεRI and the release of histamines, basophils are recruited though H_4 receptors to the nasal tissue which are subsequently activated through FcεRI in the nasal mucosa in an allergen specific manner [51-53]. Furthermore, prostaglandin D_2 has been identified as an important mediator during the EPR that signals through its receptor, CRTh2. Selective blockade of CRTh2 receptors led to the prevention of development of both early and late phase responses to intranasal allergen challenge [54].

Late phase allergic response

Predominant late phase symptoms are nasal blockage and to a lesser extent watery nasal discharge. Depending on patient susceptibility and allergen dose, allergic individuals go on to develop a late phase nasal allergic response. In contrast to the lung, nasal late responses are manifest largely as continuous symptoms and falls in peak nasal inspiratory flow at 4-12 hours (Figure 2). Mediators released during the EPR mainly histamine, PDG_2 and leukotrienes induce the influx and activation of various inflammatory cells leading to late phase response [30, 55]. Influx of inflammatory cells towards the nasal mucosa is facilitated by adhesion molecules such as vascular cell adhesion molecule 1, E-selectin and intercellular adhesion molecule 1 that promote adherence of circulating eosinophils to endothelial cells. Chemoattractants and cytokines such as IL-5 promote the infiltration of eosinophils, basophils and T cells from the systemic circulation into the nasal submucosa [56-58].

Recently, circulating ILC2s have been shown to increase following nasal allergen provocation and during seasonal allergen exposure in allergic rhinitis compared to healthy subjects. ILC2s represent alternative Th2-cytokine-producing cells in addition to mast cells, basophils and T cells that may contribute to ongoing nasal allergic inflammation [59, 60].

Immunohistochemistry of nasal turbinate biopsies from patients with allergic rhinitis obtained 6 hours after allergen challenge or during natural exposure have revealed increased expression of the lymphocyte chemokine receptors CCR3, CCR4, infiltration by eosinophils and elevated levels of cells expressing mRNA for IL-4 and IL-5 [36, 37, 61-63]. Furthermore, induction of rhinitis symptoms after grass pollen nasal allergen challenge showed an increase in activation markers expressed on peripheral blood basophils, plasmacytoid dendritic cells and memory T cells at 6 hours indicating induction of not only local but also systemic events reflecting *in vivo* activation of Th2 cells [48]. Cytokines released from basophils, mast cells and Th2 cells such as IL4, IL-5, IL-9 and IL-13 play an important role in the late phase response. Recently, it has been demonstrated that there is an inverse correlation between both IL-5 and IL-13 with nasal patency post challenge [31, 49]. Both IL-5 and IL-4 play central roles in eosinophil recruitment and activation leading to mucosal influx and the release of granule-derived positively charged proteins such as major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO). These are known to be toxic to respiratory epithelium promoting increased oxidative stress leading to epithelial injury and tissue damage. This in turn leads to the release of epithelial-derived chemokines, cytokines and growth factors that facilitate persistence of late phase responses and ongoing allergic inflammation [55, 64, 65]. IL-13 shares many activities with IL-4 including usage of a common receptor subunit (IL-4Rα-chain). IL-13 is released from mast cells, basophils and ILC2s and promotes B cells to switch in favour of IgE synthesis [66-68]. Collectively,

mobilisation of effector cells may contribute to the inflammatory features seen during late phase responses (Figure 2).

Priming effect:

Some allergic rhinitis subjects begin experiencing nasal symptoms just a few days after the onset of the pollen season while others have increasingly severe symptoms towards the end of the pollen season despite decreasing aeroallergen levels [69]. This phenomenon is termed ***priming effect*** in that the allergen dose needed to elicit nasal symptoms decreases with the repetitive natural allergen exposure [70]. Thus the birch pollen season may 'prime' the nasal mucosa in dual sensitive patients for a vigorous early onset of grass pollen-related symptoms whereas high peak seasonal pollen counts may prime for persistent symptoms at lower counts towards the end of the season [71]. This was also observed following nasal provocation when 3 day repetitive allergen challenge using ragweed induced increased nasal symptoms on sequential nasal challenges which were associated with an increase of mediator release from the influx of inflammatory cells [72]. Furthermore, recently [73] it has been demonstrated that on localized unilateral repetitive nasal allergen challenge there is an increase in nasonasal reflex and nasal-ocular symptoms with an increase in the inflammatory response after each allergen challenge supporting the existence of priming in response to local nasal allergic inflammation. Both inflammatory cells and nasal symptoms were effectively reduced after pretreatment with intranasal corticosteroids, as a consequence of inhibition of nasal priming. The concept of priming has provided a rationale for the early pre-seasonal introduction of intra-nasal steroids in the treatment of seasonal allergic rhinitis in order to prevent prolonged late phase responses that could otherwise lead to progressive inflammation of the nasal mucosa that underlies the priming effect [73-75].

Remodeling

Chronic inflammation is considered to be key factor that leads to tissue structural remodelling [76, 77]. Upper and lower respiratory airways possess a similar respiratory epithelium and comparable Th2-driven IgE-dependent inflammation that underlies the induction of allergic respiratory symptoms. Whereas airway inflammation and remodeling are characteristic of asthma, the presence/absence and extent of tissue remodeling in the upper airways in allergic rhinitis is controversial [78, 79].

A recent study looked into epithelial to mesenchymal transition (EMT) process in rhinitis which is believed to play an important role in inducing remodeling in asthma and other chronic airway diseases. No alteration in epithelial dedifferentiation in terms of expression of E-cadherin, cytokeratins, $MUC5AC^{+}$ goblet cells and $p63^{+}$ basal cells was observed, either at protein or mRNA levels between allergic rhinitis sufferers and healthy controls [80]. It has been suggested that these differences between upper and lower allergic airways may occur as a consequence of their different embryologic origin [81]. A recent study explored morphologic and immunohistochemical evidence of remodelling in patients with severe persistent allergic rhinitis (ARIA classification) compared to normal healthy controls. It was shown that despite severe nasal symptoms and the presence of persistent upper airway allergic inflammation there was no evidence of associated upper airway structural remodelling, as judged by the morphological features of the epithelium and basement membrane zone, nor by the appearances of the nasal blood vasculature and lymphatic vessels. Similarly there was no evidence of excess collagen deposition in the nasal mucosa compared to healthy controls [82] (Figure 3). These data suggest that whereas Th2 driven allergic inflammation is a feature of allergic rhinitis, the lack of evidence for remodeling in the same subjects provides limitations on the concept of the 'united airway' and question whether a causal link exists between allergic rhinitis and asthma. These findings are consistent with the findings of two recent randomised controlled trials [83, 84] that showed that treating rhinitis

with intranasal corticosteroids in asthma effectively treats their rhinitis symptoms whilst having no impact on their asthma control.

Influence of treatment on allergic rhinitis:

Avoidance of environmental allergens such as dust mites, pets and certain medications and irritants may reduce rhinitis symptoms. However, it is challenging and not feasible to consistently avoid outdoor allergens such as pollen and moulds. Recent meta-analyses showed available environmental/chemical interventions (e.g acaricides, impermeable bed covers) are not effective [85, 8].

Current treatment for controlling allergic rhinitis symptoms involves antihistamines and corticosteroids. Intranasal steroids are the most effective available medication that suppress all rhinitis symptoms including nasal blockage. It has been demonstrated that intranasal steroids decrease eosinophil infiltration with suppression of local nasal mucosal IL-4 mRNA and IL-5 mRNA expressing cells in seasonal rhinitis compared to placebo as determined by in situ hybridisation (Figure 4-A) [87, 88].

Allergen immunotherapy is currently accepted as the only mode of treatment that can reduce allergic rhinitis symptoms and modify the disease which is associated with production of functional blocking allergen-specific IgG4 [89-91]. Grass pollen immunotherapy decreases seasonal influx of eosinophils with the reduction of IL-5 mRNA expression in local nasal mucosa and a reduction in symptoms [92, 93]. Furthermore, allergen immunotherapy induces local IFN-gamma and IL-10 mRNA with an increase in IFN-gamma/IL-5 ratio in nasal mucosa which is accompanied by clinical improvement [94, 95] (Figure 4-B).

Local Allergic rhinitis

Local production of IgE in the nasal mucosa is well-documented in allergic rhinitis individuals who have raised serum specific IgE and positive skin prick tests to clinically relevant allergens [96-99]. There is a small proportion of allergic rhinitis sufferers who get typical allergic symptoms on allergen exposure in the absence of evidence of systemic IgE-sensitisation as reflected by negative skin prick tests to a panel of common aeroallergens and absence of circulating allergen-specific IgE antibodies to clinically relevant allergens. First evidence of local allergic rhinitis (LAR) was reported by Huggins and Brostoff who demonstrated positive nasal allergen provocation tests with house dust mite extract in individuals with typical allergic symptoms and negative skin prick tests to mite [100]. A number of studies have since confirmed this condition where allergic responses are confined to the target organ in the absence of evidence of systemic atopy [101-103].

For example in studies involving non-atopic subjects who underwent nasal allergen challenge, patients developed rhinitis symptoms after exposure to a variety of allergens including HDM, grass and olive pollen accompanied by positive objective measures such as changes in acoustic rhinometry and anterior rhinomanometry [104-106]. It has been suggested that up to 47% of so-called 'idiopathic' rhinitis sufferers may have local allergic rhinitis [107] whereas others have suggested that the incidence may be much lower [99]. In the study by Rondon et al, local inflammatory biomarkers such as tryptase peaked at 15 minutes and eosinophilic cationic protein significantly increased at 15 minutes and remained elevated for 24 hours after challenge in half of the LAR patients. Local grass pollen and HDM–specific IgE were also found to be increased from nasal secretions in 21-30% of these LAR patients following nasal allergen challenge [106,108]. Currently there are no studies that demonstrate local production of tissue specific IgE^+ B cells or memory B cells in Local allergic rhinitis individuals as has previously been demonstrated as the local source of IgE in typical allergic rhinitis associated with raised serum IgE [98, 109,110]. These data suggest

that in subjects who exhibit allergic rhinitis symptoms on allergen exposure without systemic sensitization to a particular allergen, then local allergic rhinitis should be considered in the differential diagnosis and indicate the need for local provocation testing with relevant allergens [111,112].

Non-allergic Rhinitis

Non-allergic rhinitis is a heterogeneous group of disorders involving chronic symptoms such as sneezing, rhinorrhea, nasal congestion, and post-nasal drainage with no obvious allergic trigger from the history, negative skin tests and negative specific IgE against common aeroallergens (Table 1). Non-allergic rhinitis has been classified into inflammatory and non-inflammatory subtypes.

Non-allergic rhinitis with Eosinophilia syndrome (NARES)

NARES typically comes on in adulthood and is more common in females. It is characterised by persistent rhinitis symptoms of sneezing, congestion, pruritis, occasional loss of smell and profuse watery rhinorrhoea. Nasal smears demonstrate increased numbers of eosinophils, typically 5-25% or more of total cell counts [113,114]. Previous studies of nasal biopsies in NARES have demonstrated increased numbers of mast cells with bound IgE and increased local tryptase levels [115]. Typically there are no allergic triggers although by current standards the diagnosis of local allergic rhinitis should be explored and the value of local nasal allergen provocation testing considered. However, NARES appears to be a distinct entity that occurs more commonly in females, is manifest as severe symptoms which are none-the-less steroid responsive. A proportion of such patients may go on to develop asthma, Samter's Triad (asthma, nasal polyps and aspirin sensitivity) or Churg-Strauss Syndrome, such that NARES patients should be followed up and monitored long term.

Non-allergic rhinitis without Eosinophilia

This is the most common form of non-allergic/idiopathic rhinitis (formerly termed vasomotor rhinitis) and is a diagnosis of exclusion. The typical clinical presentation is one of mainly clear rhinorrhoea and/or nasal obstruction as dominant symptoms in which allergic disease, sinusitis/nasal polyposis, anatomic abnormalities, pharmacological (iatrogenic), endocrine or known infections have been excluded. Patients have increased sensitivity to environmental triggers such as changes in temperature, air conditioning, pollutants and tobacco smoke and other irritants. In a proportion emotional stress, sexual arousal and alcohol may be exacerbating factors. Typically this condition responds poorly to corticosteroids. The pathophysiology underlying this disorder in incompletely understood, but there are some current observations that might lead to a better understanding of this condition [116].

In patients with typical idiopathic non-allergic rhinitis the local application of capsaicin was effective in suppressing symptoms for up to 6 weeks whereas there were no changes in local leukocyte populations, including T cells. Conversely, in patients with non-allergic rhinitis, topical corticosteroids reduced T cell numbers but had no impact on symptoms [117,118].

On unilateral cold dry air nasal challenge, non-allergic rhinitis sufferers showed a crossed nasal lacrimal reflex response with increased nasal secretion on both ipsilateral and contralateral sides to the challenge. This was effectively suppressed by topical atropine application demonstrating the nasonasal neural reflex mechanisms in rhinitis which may in part be mediated by efferent cholinergic stimulation in response to an environmental stimulus [119-121]. Subjects who were exposed to odours (vanilla, hickory smoke representing distinct and specific olfactory stimuli) underwent functional magnetic resonance imaging. During exposure there was an increase in blood flow specifically to the odor-sensitive brain regions, suggesting that a neurological response is critically involved in the pathogenesis of

NAR [122]. Furthermore, recent results demonstrated that nasal hyper-reactivity is as common in NAR as in AR, but importantly, no inflammatory cells or mediators are present [123]. These data emphasise the non-inflammatory nature of this condition and suggest that in a subgroup of patients with non-allergic rhinitis, neuronal functional abnormalities may be responsible for their symptoms.

Summary and Conclusion

The heterogeneity with multiple aspects of rhinitis pathophysiology has been summarised in this review. In conclusion, up to date evidence shows that imbalance in innate and adaptive immunity together with environmental factors is likely to play major roles in pathophysiology of rhinitis. The role of epithelium and its interaction with newly defined ILC2s through epithelial derived TSLP and IL33 cytokines plays a central role in development and progression of nasal inflammation. Developing therapeutic strategies which dampen their pathological activity remains an important goal.

Nasal tissue remodeling does not seem to be a feature of allergic rhinitis. We do need to continue to explore the lack of remodelling in allergic rhinitis and its link with innate and adaptive immunity which might shed light on newer and better treatment of remodeling. More evidence of localized allergic (LAR) and non-allergic rhinitis (NARES/NARS) are needed to shed light on mechanisms underlying different pathophysiology of chronic non-allergic rhinitis that could lead to patient tailored diagnosis and treatment.

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Legends:

Figure 1.

Activated/damaged epithelial cells secrete TSLP and IL33 that activates dendritic cells directly or through ILC2s which captures antigens, migrate to the draining lymph nodes and presents to naive T-cells inducing effector Th2 cells. Allergen activated Th2 cells in local lymph nodes secretes IL-4 that promotes class switching to IgE production by B cells. Re-exposure of the sensitized allergen leads cross-linking of IgE–FcεRI complexes on DC's, mast cells and basophils activating these cells to release of inflammatory mediators causing classic allergic reactions. Other Th2 cytokines such as IL-5, 9 and 13 are responsible for propagation and maintaining late phase allergic inflammation.

Figure 2:

Summary of mechanisms associated with EPR and LPR during the nasal allergen challenge in allergic rhinitis. Mediators released during the EPR (histamine, PDG2 and leukotrienes-blue, brown circles) induce influx and activation of inflammatory cells. Chemoattractants, histamine receptors and cytokines such as IL-5 released by effector cells during the EPR promote the infiltration of eosinophils, basophils and T cells from the systemic circulation into the nasal submucosa. Cytokines released from basophils, mast cells and Th2 cells such as

IL4, IL-5, IL-9 and IL-13 play an important role in the late phase response. NAC: Nasal allergen challenge, PD2: Prostaglandin 2.

Figure 3: Th2 cytokine (IL-4, IL-5, IL-13) levels from nasal lavage comparing persistent allergic rhinitis and healthy controls (A-D). Blood and lymphatic vessels, and collagen area stained using immunohistochemistry (E-F/G-I), respectively, comparing persistent allergic rhinitis (par) and controls.

Figure 4:

A) Effect of intranasal steroids on allergic rhinitis nasal mucosa and inflammation. PL: Placebo, INS: Intranasal steroids, EG2: Monoclonal antibody that recognises activated eosinophils. B) Effect of specific allergen immunotherapy (SIT) on allergic rhinitis nasal mucosa and inflammation. PL: Placebo, SIT: Specific allergen immunotherapy, EG2: Monoclonal antibody that recognises activated eosinophils. C-E) Pictures depicting nasal mucosal eosinophil cells, mRNA IL-5 and IL-10 using immunochemistry and *in-situ* hybridisation staining technique, respectively.

Table 1: Rhinitis phenotypes

I.	**Allergic Rhinitis**
	Allergic rhinitis with systemic sensitization
	Local allergic rhinitis without systemic sensitisation
II.	**Non-Allergic rhinitis**
	Vasomotor Rhinitis: Irritants triggered, cold air, Exercise
	Infectious
	Gustatory (Induced by spicy foods)
	Non allergic Rhinitis with Eosinophilic Syndrome (NARES)
	Occupational rhinitis
III.	**Other rhinitis syndromes**
	Drug induced rhinitis: rhinitis medicamentosa, oral contraceptives, aspirin/NSAID
	Estrogen induced: pregnancy, menstrual cycle related
	Atrophic rhinitis
	Rhinitis associated with auto-immunologic disorders (e.g, Vasculitis)

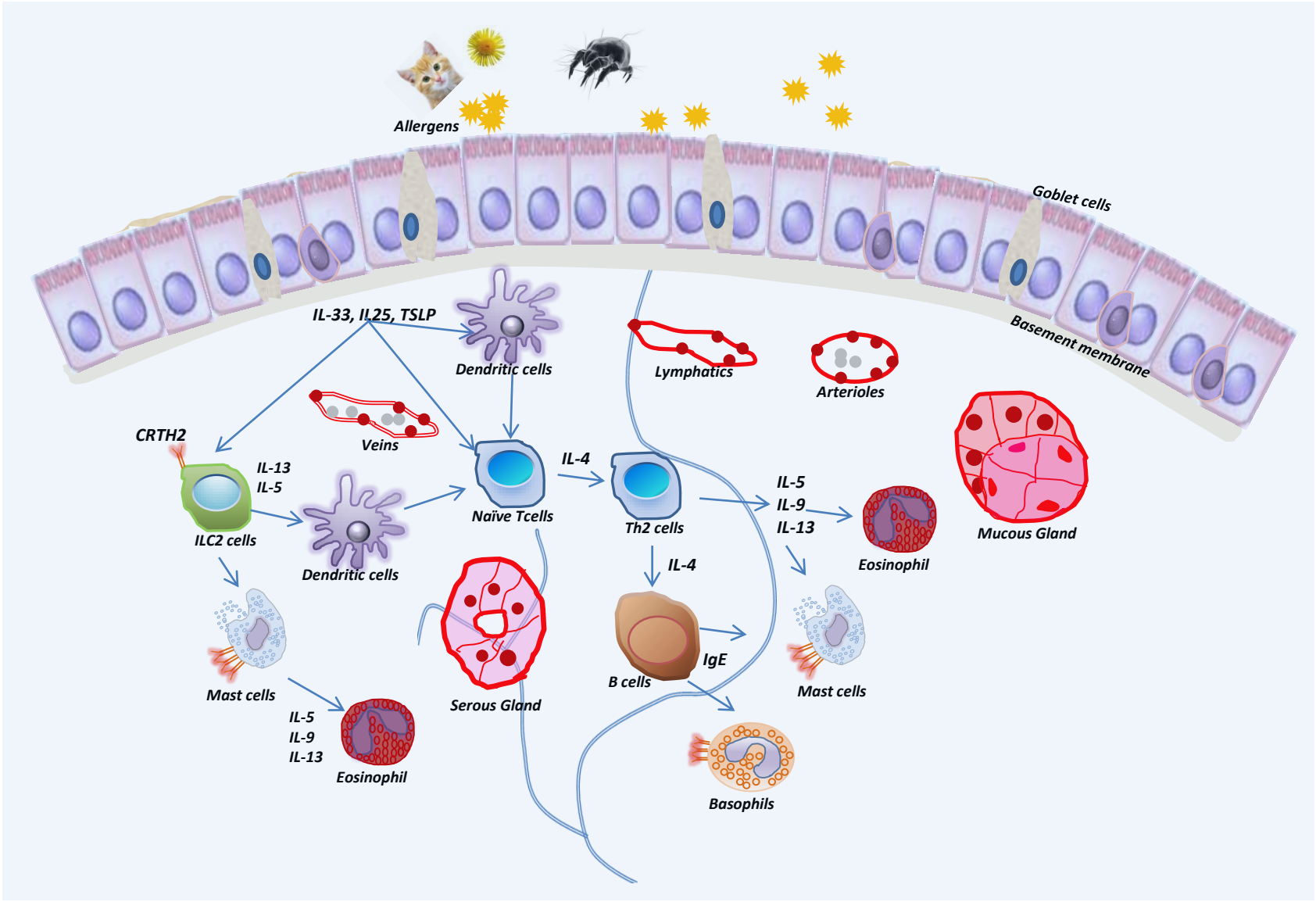

Allergens
Goblet cells
Basement membrane
IL-33, IL25, TSLP
Dendritic cells
Lymphatics
Arterioles
Veins
CRTH2
IL-13
IL-5
ILC2 cells
Dendritic cells
Naïve Tcells
IL-4
Th2 cells
IL-5
IL-9
IL-13
Eosinophil
Mucous Gland
IL-4
Mast cells
Serous Gland
B cells
IgE
Mast cells
IL-5
IL-9
IL-13
Eosinophil
Basophils

Fig 1:

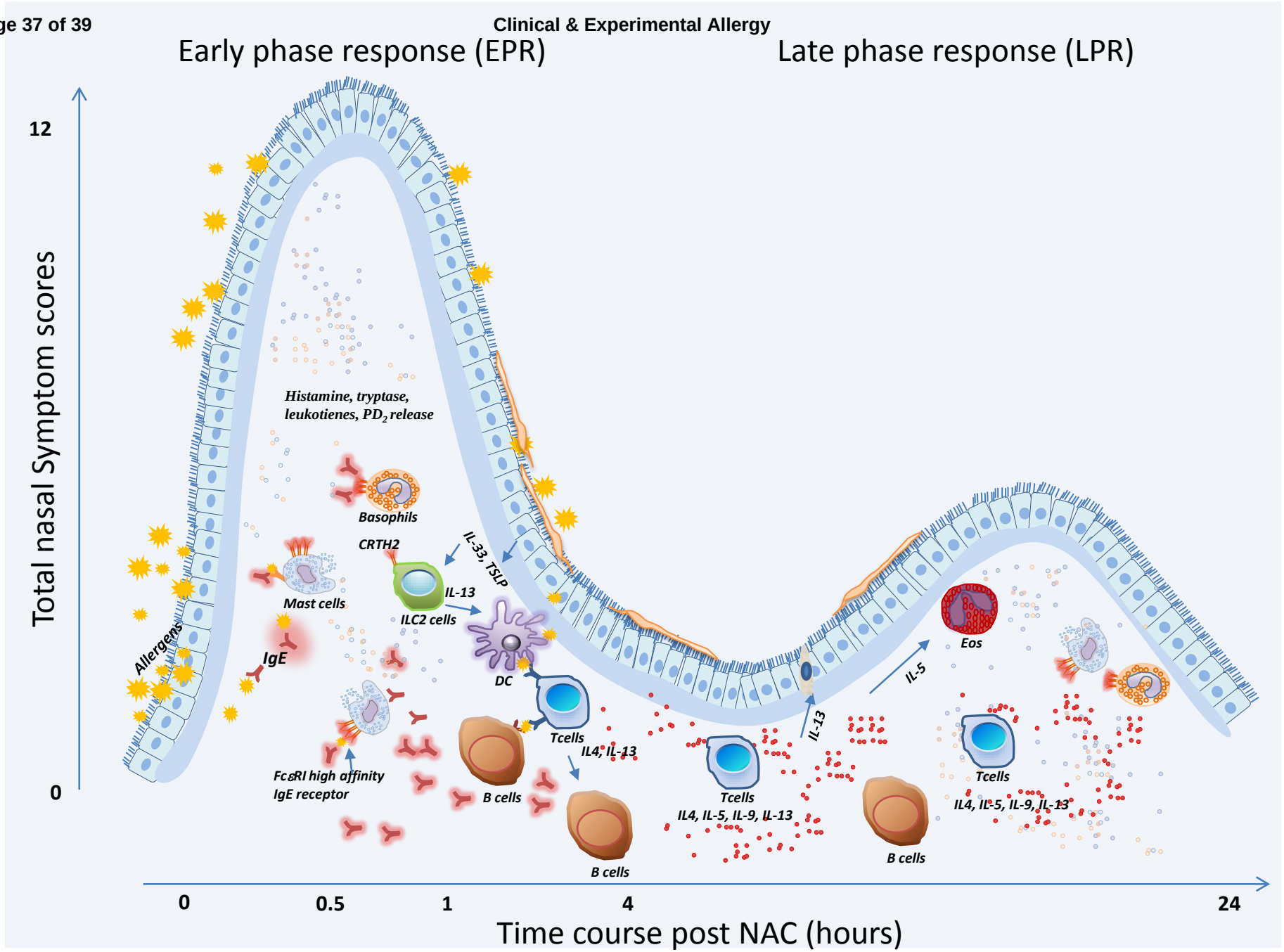

Early phase response (EPR)
Late phase response (LPR)
Total nasal Symptom scores
12
0
Histamine, tryptase, leukotienes, PD2 release
Basophils
CRTH2
IL-33, TSLP
IL-13
ILC2 cells
Mast cells
Allergens
IgE
DC
Tcells
IL4, IL-13
FcεRI high affinity IgE receptor
B cells
Tcells
IL4, IL-5, IL-9, IL-13
B cells
IL-13
IL-5
Eos
Tcells
IL4, IL-5, IL-9, IL-13
0
0.5
1
4
24
Time course post NAC (hours)

Fig 2:

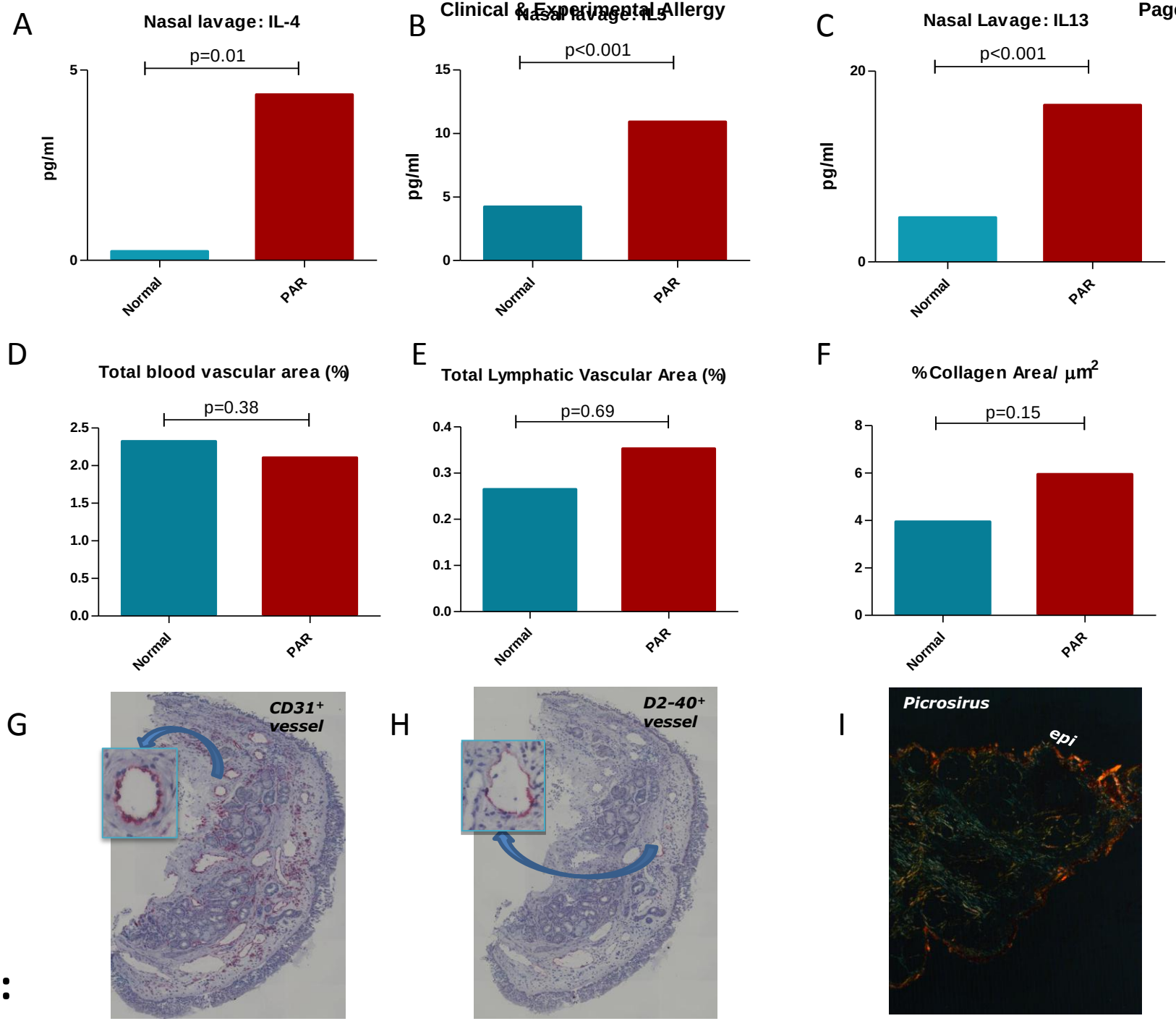
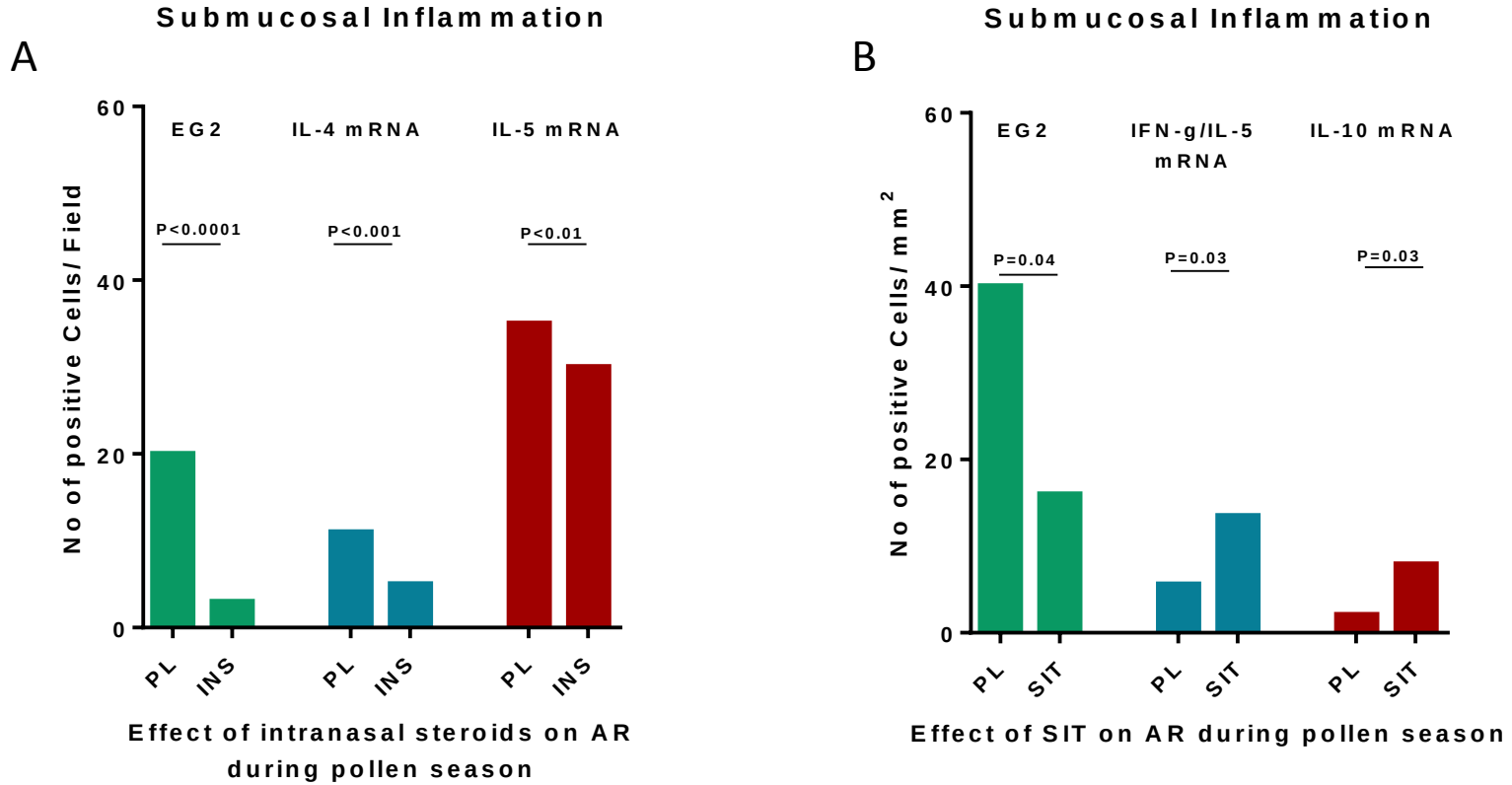
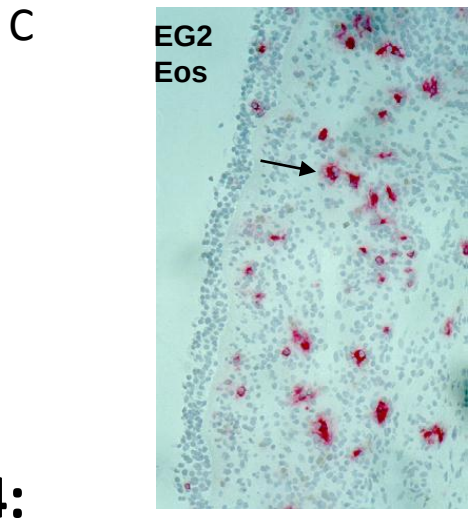
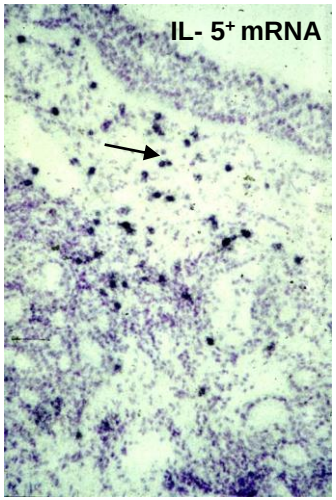

A
Nasal lavage: IL-4
p=0.01
pg/ml
5
0
Normal
PAR
B
Nasal lavage: IL5
p<0.001
pg/ml
15
10
5
0
Normal
PAR
C
Nasal Lavage: IL13
p<0.001
pg/ml
20
0
Normal
PAR
D
Total blood vascular area (%)
p=0.38
2.5
2.0
1.5
1.0
0.5
0.0
Normal
PAR
E
Total Lymphatic Vascular Area (%)
p=0.69
0.4
0.3
0.2
0.1
0.0
Normal
PAR
F
%Collagen Area/ µm2
p=0.15
8
6
4
2
0
Normal
PAR
G
CD31+ vessel
H
D2-40+ vessel
I
Picrosirus
epi

Fig 3:


Submucosal Inflammation
A
EG2
IL-4 mRNA
IL-5 mRNA
P<0.0001
P<0.001
P<0.01
No of positive Cells/ Field
60
40
20
0
PL
INS
PL
INS
PL
INS
Effect of intranasal steroids on AR during pollen season
Submucosal Inflammation
B
EG2
IFN-g/IL-5 mRNA
IL-10 mRNA
P=0.04
P=0.03
P=0.03
No of positive Cells/ mm2
60
40
20
0
PL
SIT
PL
SIT
PL
SIT
Effect of SIT on AR during pollen season


C
EG2
Eos


D
IL- 5+ mRNA

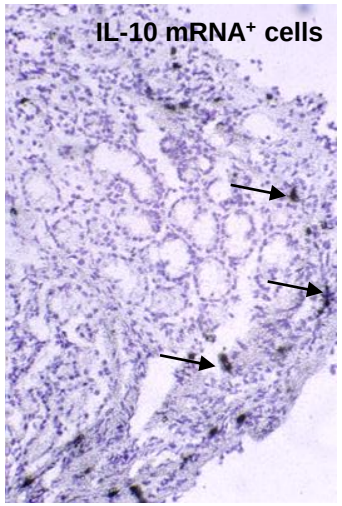

E
IL-10 mRNA+ cells

Fig 4: