Published in final edited form as:

Immunol Allergy Clin North Am. 2016 November ; 36(4): 669–680. doi:10.1016/j.iac.2016.06.004.

AERD as an Endotype of Chronic Rhinosinusitis

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Synopsis

Aspirin-Exacerbated Respiratory Disease (AERD) and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) are both diseases characterized by the presence of chronic sinonasal inflammation and nasal polyps. Both diseases are associated with asthma; AERD by definition and CRSwNP by common comorbidity (~50%). Therefore, the most prominent clinical feature distinguishing patients with AERD from those with CRSwNP remains the development of an upper or lower respiratory tract reaction following the ingestion of a COX-1 inhibitor. However, even in the absence of COX-1 inhibitors, there are other notable clinical and pathophysiological differences between AERD and CRSwNP patients. Patients with AERD on average have worse upper respiratory disease with increased sinonasal symptoms, mucosal inflammation and requirements for revision sinus surgery when compared to patients with CRSwNP. While no single genetic factor has been identified in either CRSwNP or AERD pathogenesis to date, many studies have evaluated whether there are differences in the underlying cellular and molecular mechanisms that account for the observed clinical variations. Studies from several laboratories have discovered important differences in the metabolism of arachidonic acid, including increased activity of the 5-lipoxygenase pathway and decreased levels of the anti-inflammatory prostanoid PGE₂. Clear evidence for activation of platelets in AERD also distinguishes it from CRSwNP. Nasal polyp tissues from both AERD and CRSwNP are characterized by type-2 inflammation but there are significantly increased levels of eosinophil and mast cell degranulation products in AERD sinonasal tissue, and recent evidence suggesting that spontaneous activation of eosinophils, basophils and mast cells occurs.

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Disclosures:

Whitney Stevens has no financial conflicts of interest. Robert Schleimer has served as a consultant with several pharmaceutical companies with interest in CRS, including Astra-Zeneca, Genentech, GSK, Intersect ENT, Merck, Regeneron and Sanofi. Dr. Schleimer is a founder, shareholder and advisor for Allakos.

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Keywords

Chronic Rhinosinusitis; Chronic Rhinosinusitis with Nasal Polyps; CRSwNP; Aspirin-Exacerbated Respiratory Disease; AERD; Samter's Disease; Samter's Triad

Introduction

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Aspirin-Exacerbated Respiratory Disease (AERD) are both conditions characterized by the presence of chronic sinonasal inflammation and nasal polyps. Numerous groups have labored to describe the clinical features of these diseases as well as investigate the underlying mechanisms that could be driving their overlapping but distinct pathophysiologic mechanisms. However, there are few head-to-head studies directly comparing the sinonasal inflammatory environment of CRSwNP with that of AERD. As a result, the relationship between CRSwNP and AERD remains incompletely defined.

Classification

To further understand the relationship between CRSwNP and AERD, it is important to review the clinical criteria needed to make the diagnosis of each condition. Per the consensus guidelines, patients with CRSwNP must present with greater than 12 weeks of rhinorrhea, facial pressure or pain, nasal congestion, and/or a reduction in sense of smell ^{1,2}. Additionally, there must be objective evidence of nasal polyps and mucosal disease visualized upon sinus CT imaging or nasal endoscopy. CRSwNP can exist without medical comorbidities but more often is observed with other chronic conditions such as asthma, hay fever, cystic fibrosis, or eosinophilic granulomatosis with polyangiitis.

The clinical diagnosis of AERD is based upon evolving criteria. In 1922, Widal published the first study describing a patient with asthma, nasal polyps, and sensitivity to aspirin. Later, Samter and Beers described a cohort of aspirin-sensitive patients of whom 85% had only respiratory symptoms and 51% had nasal polyps ³. In this report, it was noted "that every patient does not necessarily present with every potential component of the syndrome". Furthermore, later studies suggested that AERD patients first developed upper respiratory tract symptoms which progressed to involve the lower respiratory tract and then lastly acquired the aspirin intolerance ⁴. In 2001, the term "aspirin-exacerbated respiratory disease" was termed by Stevenson and colleagues to emphasize that these patients had underlying respiratory disease that was worsened but not induced by aspirin ⁵. Additionally, over the course of time, it was also discovered that all medications that inhibit the cyclooxygenase-1 (COX-1) enzyme, not just aspirin, could elicit upper and lower respiratory tract symptoms in AERD patients.

Given this history, it is not surprising that different terminologies are still used to define the same or related clinical phenotypes (*e.g.* Samter's Disease, Samter's Triad, AERD, NSAID-exacerbated respiratory disease (NERD), aspirin-intolerant asthma). However, even when the same terminology is used, there can be variations in the clinical features of the study cohort. For example, AERD has been investigated in patients with asthma and aspirin

intolerance as well as in patients with asthma, aspirin intolerance, and CRSwNP. How the presence (or absence) of sinonasal inflammation might influence the overall disease pathology is not known. As a result, it is not clear whether these two groups are distinct subsets or rather part of a disease continuum. Unless otherwise specified, this review will define AERD as the presence of the triad of CRSwNP, asthma, and worsening of upper and lower respiratory tract symptoms following the ingestion of COX-1 inhibitors.

Epidemiology

By definition, all patients with AERD have CRSwNP. However, not all patients with CRSwNP have AERD. It is estimated that only ~10% of patients with nasal polyps and ~9% of patients with chronic rhinosinusitis have AERD⁶. However, the true prevalence of AERD in the general population or among patients with both chronic rhinosinusitis and nasal polyps (CRSwNP) is still unknown. This is partly due to the lack of epidemiological studies evaluating patients with CRSwNP in large primary care populations.

As an additional layer of complexity, both AERD and CRSwNP are associated with asthma. Nearly all AERD patients and ~26–63% of CRSwNP patients have asthma^{1, 7, 8}. In contrast, only ~7–10% of asthmatics have AERD but as many as 90% of asthmatics may have radiographic evidence of sinonasal inflammation, with or without nasal polyps^{1, 6, 9, 10}. Interestingly, the prevalence of AERD can increase to ~15% among severe asthmatics^{6, 9} and a significant association between severe asthma and enhanced sinonasal inflammation has been reported¹¹. However, the true prevalence of AERD among patients with both CRSwNP and asthma is not known and, as a result, further investigation is needed.

Clinical Features

The respiratory reaction following ingestion of a COX-1 inhibitor is the most prominent and definitive clinical feature distinguishing patients with AERD from those with CRSwNP. In AERD patients, this reaction is associated with distinct pathophysiological changes within the sinonasal mucosa. Consequently, most AERD patients typically avoid taking COX-1 inhibitors of their own accord. This results in the presence of a population of patients with CRSwNP and asthma who have aspirin sensitivity that does not appear in their health records. Thus, diagnosis of AERD by examination of medical record charts can overlook a significant number of AERD patients.

It has been reported that as many as 15% of asthmatic patients previously unaware of having a COX-1 inhibitor hypersensitivity had a positive reaction to aspirin during an oral challenge⁴. Additionally, in separate smaller studies of patients with both CRSwNP and asthma, 20–42% had positive aspirin challenges despite being previously unaware of any COX-1 hypersensitivity^{12, 13}. In contrast, it has been estimated that as many as 15% of patients with a clinical history consistent with the triad of AERD actually do not react to aspirin upon clinical challenge and instead have only CRSwNP with asthma^{4, 13, 14}. Taken together, these studies illustrate the limitations in distinguishing CRSwNP and AERD by clinical history alone and highlight the importance of confirming the diagnosis by oral aspirin challenge.

There are other less definitive clinical features that can help to distinguish between AERD and CRSwNP. Both CRSwNP and AERD develop in adulthood, with the average age of onset being approximately 42 and 34 years respectively ^{1, 14}. CRSwNP is more common in men while AERD is more common in women ^{1, 4, 14}. Interestingly, a more recent study examining patients who had undergone sinus surgery at a tertiary care hospital suggests that among patients with CRSwNP, women had more severe disease than men as determined by radiographic evidence of enhanced sinus inflammation, need for revision surgery, and use of oral corticosteroids at the time of surgery ¹⁵. This is consistent with a large European cohort study that found that women with aspirin-induced asthma have more progressive upper and lower respiratory tract disease than men ⁴.

Clinically, patients with CRSwNP or with AERD both present with symptoms of nasal congestion, rhinorrhea, sinus pressure/pain, and/or hyposmia. Patients with AERD were shown to subjectively report more severe sinus symptoms than patients with CRSwNP ¹⁶. Additionally, AERD patients typically have significantly worse endoscopic sinus scores as well as radiographic evidence of sinonasal inflammation compared to CRSwNP patients ^{16–18}. Finally, AERD patients have greater risk of symptom recurrence following surgery and are more likely to undergo revision surgeries sooner and more frequently than those without AERD ^{19–21}. The average number of revision surgeries in AERD patients has been reported to range from 2.6 to 10 ^{4, 14, 21}. In contrast, one study reported that patients with CRS on average underwent 1.8 total sinus surgeries but the number of revision surgeries in CRSwNP patients specifically is not well-established ²².

In regards to lower respiratory tract disease, CRSwNP and AERD are both associated with asthma that is more severe than that in patients with asthma alone. Conversely, in patients with chronic rhinosinusitis undergoing surgery at a tertiary care facility, asthmatic patients had worse sinus scores than non-asthmatic patients ²³. Additionally, as mentioned previously, asthma severity increased with enhanced radiologic evidence of sinus severity ¹¹. In a separate study of 201 AERD patients, 45% had uncontrolled asthma ²⁴. Additionally, Morales and colleagues observed that AERD patients had a 60% increase in risk of severe asthma and 80% increase in emergency room visits compared to patients with aspirin-tolerant asthma ⁹. AERD patients had lower mean bronchodilator FEV1, more severe asthma by physician assessment, and higher intubation rates than patients without AERD ²⁵.

More recently, studies have begun to further define asthma characteristics, as there are variations within the population in regards to clinical features and overall disease severity. For example, the Severe Asthma Research Program performed a cluster analysis of over 700 patients with persistent asthma and identified 5 distinct asthma subsets ²⁶. In particular, one of these cohorts (group 5) was characterized by having the most severe asthma, lowest baseline lung function, and frequent systemic corticosteroid use ²⁶. Additionally, almost half of these patients reported a history of sinus surgery, ²⁶ again suggesting an association between asthma severity and chronic sinus disease. A similar cluster analysis was recently performed in a cohort of AERD patients, albeit only ~81% reported a history of having nasal polyps. In this analysis, 4 distinct subgroups of AERD were defined predominantly based upon levels of asthma severity ranging from mild to severe ²⁷. Interestingly, those patients with significant upper respiratory symptoms (group 1) had the highest levels of peripheral

blood eosinophils and urinary leukotrienes among all the subsets examined²⁷. It is thus clear that patients with NP and AERD have worse asthma than patients with asthma and no NP, and that patients with NP and asthma have worse NP than patients with NP and no asthma. These two diseases each appear to worsen the other.

A causal relationship between atopy and either CRSwNP or AERD is still not established and appears unlikely. It has been estimated that 51–86% of patients with CRSwNP^{8, 22} and 33–66% with AERD^{4, 14} are sensitized to at least one aeroallergen. However, it remains unclear whether allergic sensitization is associated with increased sinus disease severity^{8, 22, 23, 28, 29}.

In summary, AERD, on average, is characterized by more severe upper airway disease than CRSwNP and more significant lower airway disease than asthma. As a result of the severity of their disease, patients with AERD place a disproportionate financial burden on the healthcare system compared to patients with either CRSwNP or asthma alone³⁰. Given the heterogeneity in past AERD study populations, future investigations are needed to more extensively characterize patients with the clinical triad of AERD and directly compare them to patients with CRSwNP alone as well as with CRSwNP and asthma together. Such studies would also allow for a better understanding of the roles that gender, atopy, asthma, and intolerance to COX-1 inhibitors play in AERD versus CRSwNP.

Genetics

Since both CRSwNP and AERD develop in adulthood, neither a simple Mendelian pattern of inheritance nor a single genetic defect has been associated with either disease to date^{31, 32}. In support of this, cohort studies found that only 1% of American and 6% of European AERD patients reported a family member also having AERD^{4, 14}. Additionally, there have been several studies evaluating whether various specific gene polymorphisms are linked to AERD, although not all AERD patients evaluated in these analyses had CRSwNP (see discussion about definitions above)^{32–35}. Taken together, present data do not suggest a strong genetic component to CRSwNP or AERD but additional studies are clearly needed to definitively evaluate the role of genetic inheritance in CRSwNP and AERD.

As another means to search for potential gene expression differences between AERD and CRSwNP, Stankovic and colleagues examined and compared transcriptional gene profiles of nasal polyps extracted from patients with CRSwNP, AERD, and healthy controls through a microarray analysis³⁶. While specific gene signatures could distinguish AERD as well as CRSwNP nasal polyps from healthy sinonasal tissue, there were no significant differences in gene expression profiles between AERD and CRSwNP nasal polyps themselves. Interestingly, when compared to healthy controls, CRSwNP nasal polyps were specifically characterized by the up-regulation of met proto-oncogene and protein phosphatase 1 regulatory subunit 9B as well as by the down-regulation of prolactin-induced protein (PIP) and zinc alpha2-glycoprotein. In contrast, up-regulation of periostin gene expression was most characteristic of AERD polyps compared to healthy controls³⁶. The role these genes play in disease pathogenesis is uncertain but work from our laboratory has also confirmed a

significant overlap between gene signature profiles of AERD and CRSwNP polyps (Stevens et al., *unpublished data*).

It is also possible that epigenetic changes and/or differential levels of various proteins or non-protein inflammatory mediators could account for the clinical differences between the two conditions³⁷. Alterations in gene expression could also be occurring in the bone marrow, in primary or secondary lymphoid tissues or in other sites in AERD such that they are not detectable in NP tissue. Alternatively, unspecified external factors might be needed to induce the enhanced AERD phenotype observed in certain genetically susceptible patients with nasal polyps. As such, chronic viral infections, active smoking, and exposure to environmental tobacco smoke during childhood have all been hypothesized to play a role in the development of AERD^{38, 39}.

Disease Pathophysiology

Epithelial barrier dysfunction, exposures to pathogenic and non-pathogenic bacteria, and dysregulation of the host innate and adaptive immune responses are all thought to be important in CRSwNP pathophysiology. Unfortunately, less is known about the specific cellular and molecular mechanisms contributing to AERD pathogenesis in particular, especially at baseline when COX-1 inhibitors are not present. For example, the role of epithelial cells and the microbiome in AERD has not been as extensively characterized as it has in CRSwNP^{40–42}. As a result, it is possible that specific functional and physical defects in sinonasal epithelial cells as well as alterations in the microbiome of the sinonasal cavity could distinguish AERD and CRSwNP clinical phenotypes. Clearly, further investigations are warranted.

Host Immune Response

There has been an increasing focus on exploring how the host immune response could contribute to the chronic sinonasal inflammation seen in CRSwNP and AERD. One of the hallmarks of CRSwNP and AERD nasal polyps is an enhanced tissue eosinophilia compared to healthy sinonasal tissue⁴³. Additionally, levels of the eosinophil granule protein, eosinophil cationic protein (ECP), were also significantly elevated in both subsets of nasal polyps compared to controls as well as in AERD nasal polyps compared to CRSwNP^{43–45}. In contrast, recent studies found no significant difference in the number of eosinophils counted in hematoxylin and eosin stained slides within nasal polyp sections from AERD and CRSwNP nasal polyps^{45, 46}. Taken together, these observations lead to the hypothesis that eosinophils are more highly activated in AERD compared to CRSwNP, thus releasing their granule contents (causing more ECP to be detected in AERD) but in the process losing their ability to be detected by traditional histologic staining.

It should be noted that not all patients with CRSwNP have enhanced tissue eosinophilia. In particular, Asian patients either living in Asia or in the United States were found to have significantly less eosinophils in their nasal polyps when compared to CRSwNP patients of European descent^{44, 47}. These observations would in turn suggest that Asian patients, given their relative paucity of tissue eosinophils, might be less likely to have AERD. This is supported by one small study from China that found the prevalence of AERD to be 0.57%

among patients evaluated with CRSwNP⁴⁸, which is must lower than the 9–10% estimated in a meta-analysis of patients predominantly of European descent⁶. Second generation Asians with CRSwNP in the US also had less atopy and less comorbidity with asthma than non Asian Americans. One interpretation of these findings is that the new generation of type 2 targeting biologicals may have reduced efficacy in patients of Asian descent.

In addition to eosinophils, CRSwNP nasal polyps are also traditionally characterized as having an increased number of innate type-2 lymphoid cells (ILC2), mast cells, basophils, and neutrophils when compared to healthy sinonasal tissue^{46, 49–51}. Walford and colleagues reported an overall correlation between the number of eosinophils and ILC2s in nasal polyps but they did not specifically compare ILC2 numbers in AERD versus CRSwNP nasal polyps⁵⁰. Similar to eosinophils, mast cell numbers did not significantly differ between CRSwNP and AERD nasal polyps^{41, 52}. However, mast cells are a major source of prostaglandin D2 (PGD₂) and this inflammatory mediator has been shown to be significantly elevated in AERD compared to CRSwNP patients, especially after aspirin challenge^{52, 53}. Finally, basophil numbers were significantly reduced in AERD versus CRSwNP nasal polyps⁴⁶. It remains unclear exactly how eosinophils, basophils, mast cells, and ILC2s each contribute to sinonasal inflammation and the clinical symptoms of either CRSwNP or AERD. Furthermore, given the elevated levels of PGD₂ and ECP despite a lack of significant elevation in number of mast cells or eosinophils, it is tempting to speculate that these innate immune cells are more activated in AERD than CRSwNP. However, additional studies are needed to further evaluate this hypothesis.

Even less is known regarding adaptive immune cells in AERD. T cells are elevated in nasal polyps of CRSwNP patients compared to healthy controls^{43, 54}. Additionally, B cells and plasma cells are also elevated in CRSwNP nasal polyps and thought to be locally activated within this tissue to produce increased amounts of IgG, IgA, IgM and IgE^{43, 55–57}. Some of the antibodies found in CRSwNP nasal polyps are against self-proteins (e.g. nuclear antigens and cytokines) but it is unclear if similar levels of autoantibodies exist in AERD patients^{58, 59}.

It has been estimated that as many as 64% of CRSwNP and 87% of AERD patients are colonized with *Staphylococcus aureus* with a subset of these patients producing IgE against staphylococcal superantigens⁶⁰. Some studies report significantly increased levels of IgE to staphylococcal superantigens in AERD nasal polyps compared to CRSwNP^{61, 62} while a more recent study found no difference⁶³. Taken together, additional studies are needed to further define the relationship between IgE to staphylococcal superantigens in AERD and CRSwNP nasal polyps. However, these specific antibodies may still contribute by an unknown mechanism to the chronic sinonasal inflammation observed in both diseases. In addition, *Staphylococcus aureus* enterotoxins can activate large numbers of T cells, and there is a body of literature suggesting that T cell activation mediated by these toxins plays a role in CRSwNP^{64–66}.

Arachidonic Acid Metabolites

AERD is classically characterized by a systemic dysregulation in arachidonic acid metabolism but a full description of this pathway is beyond the scope of this review. There

have been some studies that have specifically focused on examination of prostaglandin and leukotriene mediators in the sinonasal tissue of AERD compared to CRSwNP patients. For example, levels of Prostaglandin E2 (PGE₂), along with its receptor EP₂, are decreased in AERD versus CRSwNP nasal polyps^{67–70}. Given the anti-inflammatory properties of PGE₂, its reduction in AERD could in turn contribute to the enhanced sinonasal inflammation observed.

Laidlaw and colleagues recently reported that the number of platelet-adherent leukocytes was significantly increased in AERD compared to CRSwNP nasal polyps⁷¹. Furthermore, these platelets could convert leukocyte-derived Leukotriene (LT) A₄ into LTC₄ and thus contribute to the elevated levels of cysteinyl leukotrienes that are classically seen in AERD nasal polyps compared to CRSwNP or healthy controls^{67, 71}. Furthermore, the cysteinyl leukotriene receptor, CysLT₁, is also elevated in AERD versus CRSwNP^{68, 72, 73}. Interestingly, in CRSwNP, cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) were also significantly elevated in sinonasal tissue when compared to healthy mucosae^{69, 74}. How these mediators all contribute to different clinical phenotypes in AERD versus CRSwNP is still not entirely understood.

Other Inflammatory Mediators

In addition to arachidonic acid metabolites, there have been numerous studies characterizing the baseline inflammatory milieu of nasal polyps from CRSwNP and AERD patients. Given the association with type-2 innate immune cells (e.g. mast cells, eosinophils, and basophils), it is not surprising that there are elevations in levels of traditional type-2 inflammatory mediators in AERD and also in CRSwNP nasal polyps when compared to healthy sinonasal tissue (e.g. IL-5, IL-4, IL-13, Eotaxin-1 Eotaxin-2)^{43, 44, 45, 75, 76}.

However, when directly comparing AERD nasal polyps with CRSwNP nasal polyps, there have been conflicting results. Some reports suggest that protein levels of IL-5 and the type-1 cytokine, IFN γ , are elevated in AERD compared to CRSwNP polyps^{67, 77}. More recently, a separate study evaluated the expression of 19 different inflammatory mediators in AERD and CRSwNP polyps. Surprisingly, there were no differences in levels of type-2 cytokines (IL-4, IL-5, IL-13, Eotaxin-1, Eotaxin-2, and MCP-4) or type-1 cytokines (IL-6, IFN γ) between these diseases⁴⁵, although levels of GM-CSF and MCP-1 were significantly elevated in AERD nasal polyps⁴⁵. It is unclear why there are discrepancies among studies but possible explanations could include differences in the tissues collected, techniques utilized to measure protein levels, the use of corticosteroids or other drugs within the study populations etc.

In summary, it appears that both CRSwNP and AERD are characterized by a type-2 inflammatory milieu with increased levels of both type-2 cytokines and eosinophils when compared to healthy sinonasal tissue but not necessarily when compared to each other. There is a marked increase in levels of certain mediators released by activated innate immune cells (e.g. ECP and PGD₂) in AERD compared to CRSwNP. While the underlying mechanisms that contribute to the increase in inflammatory cell degranulation products is unknown, it is worth exploring whether the abnormalities in arachidonic acid metabolism or other factors mediate the exaggerated activation of these cells in AERD.

Summary

CRSwNP and AERD are both important clinical diseases associated with increased socioeconomic burden and decreased quality of life. The most prominent clinical feature distinguishing patients with AERD from those with CRSwNP remains the development of an upper or lower respiratory tract reaction following the ingestion of a COX-1 inhibitor. However, even in the absence of COX-1 inhibitors, there are other clinical and pathophysiological differences observed between AERD and CRSwNP patients. Those with AERD on average have worse upper respiratory disease with increased sinonasal symptoms, mucosal inflammation and requirements for revision sinus surgery when compared to patients with CRSwNP. While no single genetic factor has been identified in either CRSwNP or AERD pathogenesis to date, studies characterizing differences in the underlying cellular and molecular mechanisms that could account for the observed clinical variations are progressing. Both AERD and CRSwNP nasal polyps are now known to be characterized by a type-2 inflammatory environment but there appear to be significantly increased levels of eosinophil and mast cell degranulation occurring in AERD sinonasal tissue. In addition, AERD, unlike CRSwNP, is also characterized by the systemic dysregulation of arachidonic acid metabolism and activation of platelet function. The underlying mechanisms that contribute to these observations are still not fully known and additional studies are needed to further define both CRSwNP and AERD pathogenesis.

Acknowledgments

Funding:

This work was supported by Chronic Rhinosinusitis Integrative Studies Program (U19-AI106683) and by the National Institutes of Health grants T32 AI083216, R37 HLO68546, RO1 HL0788860 and RO1 AI104733.

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Key Points

- Clinically, patients with AERD can be distinguished from those with CRSwNP and asthma by the development of respiratory symptoms following the ingestion of a COX-1 inhibitor. However, clinical history alone may not always be sufficient to confirm the diagnosis of AERD.
- In the absence of COX-1 inhibitors, AERD patients on average still have worse upper and lower respiratory tract disease than those patients with CRSwNP with or without asthma.
- Nasal polyps from AERD and CRSwNP patients are both defined by a predominant type-2 inflammatory environment but there appears to be significantly increased levels of eosinophil and mast cell degranulation occurring in AERD.
- Mechanistically, AERD, unlike CRSwNP, is characterized by platelet activation as well as a dysregulation in arachidonic acid metabolism.