

Aspirin or Nonsteroidal Anti-inflammatory Drug—Exacerbated Chronic Rhinosinusitis



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Aspirin (ASA)-exacerbated respiratory disease (AERD) is characterized by upper airway congestion due to eosinophilic inflammation of the nasal and sinus membranes and nasal polyposis, associated with increased leukotriene production that is further accentuated by ASA or other nonsteroidal anti-inflammatory drug (NSAID) ingestion. It occurs in 5% to 10% of subjects with chronic rhinosinusitis (CRS) and in 15% to 40% of those with nasal polyposis. Although AERD with CRS is usually associated with asthma, this is not always the case. The eosinophilic airway inflammation and symptoms precede clinical reactions to ASA or other NSAIDs, but ultimately affected subjects experience worsening of symptoms with ingestion of ASA/NSAIDs. The endotypic mechanism for this worsening is related to a chronic increase in leukotriene and a decrease in prostaglandin production, particularly prostaglandin E₂, that is further aggravated by the inhibition of cyclooxygenase 1. IgE does not likely play a role in the pathogenesis of the disease although nasal and sinus staphylococcal infection increases local IgE level and may increase total IgE and specific IgE levels. Genetic studies suggest that multiple genes may be involved, but the genetic abnormalities may differ in affected subjects from different ethnicities and candidate genes have not been confirmed in multiple studies. Genome-wide association studies have not been revealing. The phenotype is recognized by the mucosal inflammation and worsening of symptoms acutely with ASA/NSAID. There is clinical improvement with ASA

desensitization followed by regular ingestion of ASA or other NSAIDs. Further understanding of this unique phenotype and endotype of CRS will likely improve the understanding of other eosinophilic airway diseases. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:590-8)

Key words: Aspirin-exacerbated respiratory disease; Leukotriene; Nonsteroidal anti-inflammatory drug; Nasal polyps; Rhinosinusitis

Aspirin-exacerbated respiratory disease (AERD) with chronic rhinosinusitis (CRS) is a phenotype of CRS defined by exacerbation of persistent nasal and sinus symptoms following the ingestion or nasal application of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase type 1 (COX-1).^{1,2} CRS with AERD is characterized by chronic eosinophilic mucosal inflammation, pansinusitis, and nasal polyposis (NP). This endotype of CRS is characterized by increased leukotriene (LT) production, which is further enhanced by NSAIDs. Most affected with AERD with CRS also have persistent asthma, but not all.^{1,3} The eosinophilic mucosal inflammation is associated with an increased expression of CD4 lymphocyte cytokines (eg, IL-4, IL-5, and IL-13) (Figure 1), but allergic sensitivity with specific IgE is not typical or required.⁴ Aspirin or other NSAID desensitization may improve the symptoms of rhinosinusitis and the mucosal inflammation.^{5,6} However, the disease develops and persists without exposure to NSAIDs. Some prefer the term NSAID-exacerbated respiratory disease rather than AERD because all COX-1 inhibitors increase mucosal inflammation; AERD with CRS will be used in this review.

DEMOGRAPHIC CHARACTERISTICS

AERD affects up to 36% to 50% of individuals with CRS and NPs evaluated in a specialty clinic, with variation based on historical definition of the disease versus confirmation with aspirin (ASA)/NSAID challenge.^{7,8} However, these numbers most likely exaggerate the prevalence because of selective referral to centers with an interest in this disease. Other estimates are that 5% to 12% of the general population experiences CRS, probably 5% or less of whom have AERD. In subjects with asthma, an estimated 4% to 12% have AERD; in subjects with asthma with CRS, 14% to 24%; and in those with NPs, up to 30% to 40%.^{9,10} A 2015 systematic review of 1770 publications concluded that the prevalence of AERD in those with asthma is 7%, in those with severe asthma is 15%, in those with NP is 10%, and in those with CRS is 9%.¹¹ Chinese populations living in China have a much lower prevalence of AERD. Many ethnic groups have this disease, but there may be differences in their pathogenesis

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Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
ASA- Aspirin
COX-1- Cyclooxygenase type 1
CRS- Chronic rhinosinusitis
LT- Leukotriene
LTE4- Leukotriene E4
NP- Nasal polypsis
NSAIDs- Nonsteroidal anti-inflammatory drugs
PGE2- Prostaglandin E2

because of genetic differences.¹ The CRS usually develops in young to middle-aged adults, equally in both males and females, with symptoms progressing over many years.

CLINICAL CHARACTERISTICS

Persistent or perennial rhinorrhea and nasal congestion refractory to pharmacotherapy are usually the first symptoms to develop in the course of the disease. The nasal symptoms usually precede the recognition of ASA/NSAID hypersensitivity by many years. The severity of chronic nasal congestion and the degree of worsening with ASA/NSAID ingestion increases with time. Specific IgE antibodies to inhaled allergens occur in approximately 30% of affected individuals, but allergen exposure usually does not correlate with symptoms of CRS. There may be symptoms of allergic rhinitis and allergic disease may be a comorbidity, but allergic symptoms are difficult to recognize and quantitate with the ongoing chronic disease. Little evidence supports the importance of an allergic response to inhaled antigens in the pathogenesis. Nasal symptoms gradually become more persistent, associated with the development of hyposmia/anosmia, noninfectious mucosal inflammation, and NPs. Asthma usually is a comorbidity, and its severity tends to increase with time. The eosinophilic nasal mucosal disease can be aggravated by infections, but chronic recurrent symptoms are largely independent of this phenomenon. Pedunculated NPs develop within several years of symptom onset but may be detected earlier if the affected subject is evaluated with rhinoscopy or imaging techniques. Bacterial debris, particularly exotoxins of *Staphylococcus aureus*, may be important in the pathogenesis of the mucosal disease, but its essential role is uncertain in AERD with CRS.^{12,13}

Symptoms of rhinorrhea, epiphora, conjunctival edema, and nasal congestion occur within 30 to 120 minutes to 3 hours after ingestion of ASA/NSAIDs and do not result from a specific immunologic response as evidenced by structurally distinct COX-1 inhibitors all causing symptoms. The severity of the symptom exacerbation is related to dose and potency of COX-1 inhibition. In addition, levels of some LTs are chronically increased, particularly in the mucosal tissue and secretions, as well as metabolic products in the urine, even without exposure to exogenous COX-1 inhibitors, suggesting a chronic pathological mechanism independent of ASA/NSAIDs. ASA/NSAID ingestion resulting in an exacerbation of nasal symptoms also results in a refractory period, lasting 2 to 4 days, during which additional ASA/NSAID, in doses similar to the exacerbating dose, can be ingested with impunity.^{6,8} Maintaining this refractory state may be related to the clinical improvement observed with low daily ASA/NSAID ingestion in affected subjects. Some investigators question the clinical benefit of ASA/NSAID desensitization,^{14,15} but many other studies support a benefit.^{16,17}

COMORBIDITIES

AERD is a generalized upper and lower airway disease with chronic rhinitis and asthma, with asthma being the major comorbidity of AERD with CRS. Typically, the asthma is moderate to severe, persistent, and corticosteroid responsive, although frequent relapses occur even without ASA/NSAID ingestion. The asthma often progresses to irreversible obstructive airway disease.¹⁸ The major sources of patient dissatisfaction in AERD with CRS are hyposmia or anosmia and chronic nasal obstruction, primarily from the polyps and mucosal membrane edema. The eosinophilic-rich polyps may enlarge with time and even create physical complications with bone erosion of the sinus or nasal cavities and complete sinus opacification (Figure 2). This is evident on radiographic imaging and occasionally visible with broadening of the nasal bridge, or saddle nose deformity. The severe nasal congestion contributes to sleep disturbance, which includes sleep disordered breathing. Headaches are not a typical feature of this disease.

PATHOPHYSIOLOGY

CRS with AERD is a distinct phenotype and endotype of CRS.^{1,19} The unique pathogenesis of AERD with CRS encompasses 2 closely related phenomena: first, chronic eosinophilic inflammation resulting in pansinusitis and nasal polyps, and second, exacerbation with COX-1 inhibition by ASA and other NSAIDs.²⁰ Limitations of the pathogenetic studies include the reduced availability of control tissue, since polyps in AERD with CRS provide a readily available source for such tissue studies, but polyps are often lacking in ASA-tolerant CRS. Turbinate or uncinate process mucosa is frequently used as a tissue control to compare with nasal polyps; however, the amount of readily available tissue in such subjects without polyps is significantly less. Furthermore, the findings may be related more to the pathogenesis of NP rather than specific to AERD with CRS.

The pathophysiology of CRS with AERD is a combination of eosinophilic nasal and sinus mucosal inflammation associated with increased LT production, increased mast cell and T_H2 mediators, and decreased prostaglandin E2 (PGE2) production (Figure 3). The primary mechanism remains unknown.

Eosinophilic mucosal inflammation

ASA/NSAID exacerbation of AERD CRS is linked to release of mast cell (eg, tryptase, histamine, and PgD2) and eosinophil mediators (eg, eosinophil cationic protein and major basic protein) based on nasal lavage of challenged subjects.^{22,23} Cytokine production in the mucosa is shared with CRS with NP without AERD but the distinctive feature of CRS with AERD is the increase in LT production and clinical exacerbation with ASA/NSAID ingestion. Mucosal eosinophils are consistently detected in AERD with CRS. Tissue eosinophils are linked to a spectrum of local cytokine production affecting eosinophils, including IL-5, GM-CSF, regulated on activation normal T cell expressed and secreted, IFN- γ , and eotaxins (chemotactic factors for eosinophils).^{24,25}

Arachidonic acid metabolism

Increased LT production is a characteristic of AERD with CRS, but some data challenge the assumption that LT production is the primary cause of this disease^{23,26} (Figure 3). Genetic studies linking LT synthesis or receptors to AERD with CRS suggest that it is a primary cause of the disease. However, *in vitro*

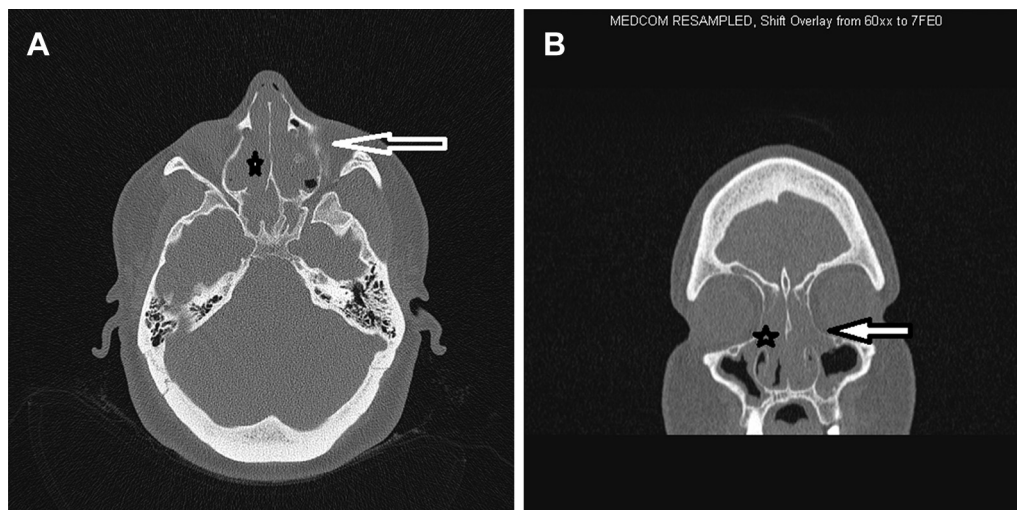


FIGURE 1. Computed tomographic scans of a patient with AERD. The polypoid inflammation is filling the nasal airway (star) and bone erosion is noted with the arrow. **A**, An axial view. **B**, A coronal view. (Images courtesy of Dr Donald Lanza of the Sinus & Nasal Institute of Florida, St Petersburg, Florida.)

LT concentrations and levels of LT synthesis enzyme mRNAs in NPs correlate with the number of eosinophils or mast cells in the tissue in both AERD and ASA-tolerant subjects.^{27,28} The sentinel importance of LT metabolism in AERD with CRS also can be challenged by the lack of selective efficacy of LT receptor antagonists in this disease compared with ASA-tolerant CRS.²⁹ Thus, LT upregulation may be a secondary phenomenon of tissue eosinophilia and activation of mast cells and not the initiator of the disease process (Figures 3 and 4).

Various arachidonic acid products are associated with AERD. Mast cells and eosinophils are the source of large amounts of LTs and prostaglandins generated from arachidonic acid (Figures 3 and 4). Both cells are prevalent within NPs from subjects with AERD with CRS. Lipoxins, an anti-inflammatory lipid substance, may be decreased, as evidenced by blood cell and NP tissue cell production from affected individuals.^{27,30} NP epithelial cells from affected subjects produce less PgE2 than do tissue from ASA-tolerant subjects.

PgE2 has a bronchoprotective effect, suggesting that it plays a role in decreasing airway hyperreactivity, mast cell activation, and eosinophil activation and chemotaxis (Figures 3 and 4). Similarly, eosinophilic inflammation in the nasal mucosa occurs with a decrease in local PgE2. The sinonasal eosinophilic inflammation would be further increased by ASA/NSAID ingestion, which would further decrease PgE2 level acutely and increase LT levels (Figure 4).^{23,31-33} Inhalation of PgE2 prevents ASA-induced bronchospasm and the increase in urinary LTE4.³⁴ The primary importance of a decrease in PgE2 is further supported by a PgE2-deficient mouse model that displays the characteristics of AERD with increased chronic LT production, eosinophilic airway inflammation, and increased LT production following ASA ingestion.³¹ Some of these research studies are performed in subjects with AERD and asthma, but the pathogenesis of the upper airway is most likely similar, if not identical, to the lower airway in subjects with AERD with CRS and subjects with AERD with asthma. The distinction may be that a second susceptibility factor specific for asthma is necessary to develop this disease. Finally, mutations in candidate genes or

hypermethylation of mRNA, suppressing transcription of PgE2 synthase and E prostanoid receptors, in AERD support dysfunction in PgE2 function.³²⁻³⁴

Platelets may also be a source of LTs.³⁵ The peripheral blood cells of affected subjects show adherent platelets on circulating neutrophils, monocytes, and eosinophils. Adherent platelets are a source of leukotriene C4 (LTC4) synthase, metabolizing leukotriene A4 (LTA4) produced by the leukocytes into cysteinyl leukotrienes. Estimates are that 50% of the total urinary leukotriene E4 (LTE4), the final metabolic product of LTs, is derived from activated platelets and the number of adherent platelets on blood cells correlates with the urinary LTE4.

Mast cells

Various independent data sources support a role of mast cells in AERD^{23,35,36} (Figures 3 and 4). Sodium cromolyn and nedocromil sodium, mast cell stabilizers, reduce bronchoconstriction with ASA/NSAID ingestion in subjects with AERD and asthma.³⁷ PgD2, a mast cell prostanoid, and its metabolites increase in both the nasal mucosa and urine following ASA ingestion. Subjects who were successfully desensitized to ASA have lower levels of urinary PgD2 metabolic products than do subjects who were not successfully desensitized, supporting a reduction in mast cell degranulation.³⁶

Specific IgE

Specific IgE to inhaled allergens occurs in approximately 30% of affected subjects; it unlikely contributes to the pathogenesis of the disease, as its presence is not necessary or sufficient to cause AERD with CRS. The potential role of local IgE production in the nasal mucosa has been suggested by the possible dysregulation of IgE production in nasal polyp tissue. Several lines of evidence suggest that bacterial products, particularly *Staphylococcus aureus* enterotoxins and exotoxins, may be superantigens and modify IgE. Such superantigens may nonspecifically activate T cells and upregulate various inflammatory mediators, including IL-4, IL-5, and IL-13. They may also increase total and specific IgE production as well as recruit eosinophils. In addition, serum

Clinical Phenotype	Cellular Phenotype	Treatment Options
Anosmia/Hyposmia	Eos +++	Topical nasal corticosteroids
Edematous polyps	IL-4, 5,13+++	LMA
Mucosal eosinophila	LT++++	Systemic corticosteroids
Pansinusitis	IL-10 (-)	Surgical polypectomy
	TGF- β (--)	ASA desensitization*
	M2 macrophages++	?Omalizumab
	Th2++	?Mepolizumab
	SA/SE/SPA++	?Dupilumab
	Local s-IgE+, SA s-IgE	???Reslizumab
	Treg (-)	
	Pg E2(--)	

Panel A.

Panel B.

Panel C.

*Aspirin intolerant subjects (Aspirin Exacerbated Respiratory Disease [AERD])

Eos: Eosinophils

ASA: Aspirin

+: Increased

IL-4: Interleukin 4

INCS: Intranasal corticosteroid

PMN: Neutrophils

IL-5: Interleukin 5

OCS: Oral corticosteroid

(-): Decreased

s-IgE: Allergen specific-IgE

LT: Leukotrienes

LTM: Leukotriene modifiers

INA: Intranasal antihistamine

LMA: Leukotriene modifiers

ID: Immunodeficiency

FIGURE 2. A listing of (A) clinical phenotypes, (B) cellular phenotypes including cellular products, and (C) treatment options. There is no significance of the order. Part B suggests potential endotypes that are defined by a specific, functional, or pathophysiological mechanism. Increased LT production is a consistent feature of AERD, but the mechanism by which this production is increased is not due to a single mechanism in all affected subjects and LT increase may be due to multiple mechanisms in a single individual. The treatment options are limited to corticosteroids, LT modifiers, NSAID desensitization, and specific biologics that target substances increased in subjects with AERD. The most effective therapies to date are corticosteroids, NSAID desensitization, and LT synthesis inhibition. mAb immune modulation has not been sufficiently studied in AERD. Adapted from Ledford et al.¹ —, Decreased; *Eos*, eosinophils; *ID*, immunodeficiency; +, increased; *INA*, intranasal antihistamine; *INCS*, intranasal corticosteroid; *LMA*, Leukotriene modifier; *OCS*, oral corticosteroid; *PMN*, neutrophils; *s-IgE*, allergen specific IgE. *Aspirin-intolerant subjects.

and polyp fluid specific IgE to *Staphylococcus* enterotoxin and superantigens correlates with polyp levels of eosinophil cationic protein (ECP), eotaxin, and IL-5.^{12,13} Thus, *Staphylococcus* may be a source of both a superantigen immunologic modulator and/or an antigen stimulator of mucosal IgE.

Specific IgE for ASA/NSAIDs has been reported, but rarely. As opposed to structural cross-reactivity, which would support an immunologic etiology, AERD with CRS is affected by various, structurally distinct NSAIDs. The importance of COX-1 inhibition in exacerbations with ASA/NSAIDs is supported by the

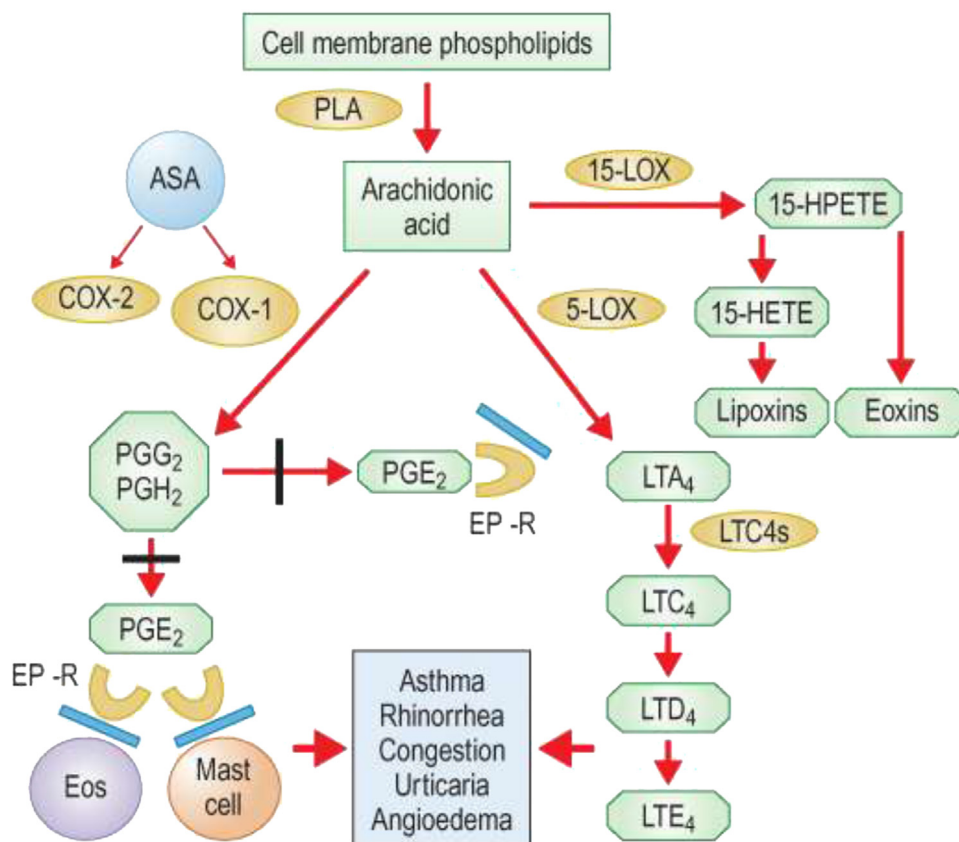


FIGURE 3. Arachidonic acid (AA) metabolism diagram, with enzymes in tan balloons, inhibitory effects of aspirin as black bars, PGE₂ receptors (prostanoid receptors) as tan semicircles, and anti-inflammatory effects of activation of PGE₂ receptor displayed by blue bars. AA is released from membrane phospholipids, primarily the second fatty acid in the glycerol backbone of phosphatidyl choline, and is metabolized into prostaglandins and LTs by specific, enzymatic pathways. AA metabolism is altered in AERD with CRS, with increased LT production primarily by mast cells, eosinophils, and platelets. 5-LOX, 5-lipoxygenase; 15-HETE, 15-hydroxyicosatetraenoic acid; 15-HPETE, 15-hydroperoxyicosatetraenoic acid; 15-LOX, 15-lipoxygenase; COX-2, Cyclooxygenase 2; Eos, eosinophils; EP-R, receptor for prostaglandin E₂; LTA₄, leukotriene A₄; LTC₄, leukotriene C₄; LTD₄, leukotriene D₄; LTE₄, leukotriene E₄; PLA, phospholipase A; PGE₂, prostaglandin E₂; PGG₂, prostaglandin G₂; PGH₂, prostaglandin H₂. (Reproduced and modified with permission from Kowalski ML. Diagnosis of aspirin sensitivity in aspirin-exacerbated respiratory disease. In: Pawankar R, Holgate ST, Rosenwasser LJ, eds. Allergy frontiers: diagnosis and health economics. New York: Springer; 2009:349-72).²¹

observation that COX-I inhibition potency of the specific provocation determines the severity of symptoms, rather than structural characteristics or immunologic recognition of a specific NSAID.^{38,39}

T Cells

A role for specific T cells in AERD with CRS is supported by the observation in one study that memory T cells (CD45RO+) are increased in nasal polyp tissue.⁴⁰ The increase in mucosal CD45RO+ T cells was associated with upregulation of the before-mentioned eosinophilic markers. These findings could be a result of the eosinophilic inflammation rather than serving a causal role. The specificity of the memory T cells is unknown.⁴⁰

TREATMENT

The initial recommendation for AERD with CRS is to avoid ASA and NSAIDs that inhibit COX-1.^{5,6,14} This proscription applies to dermal application of NSAIDs such as topical diclofenac. Acetaminophen and COX-2 inhibitors, such as celecoxib, are

generally well tolerated, and less potent COX-1 inhibitors, such as meloxicam, may be tolerated. The primary treatment of AERD with CRS is topical corticosteroid therapy to reduce the eosinophilic mucosal inflammation, nasal congestion, and the size of the NPs.¹⁴ Occasionally, the degree of nasal obstruction is of sufficient severity to limit topical therapy, and systemic corticosteroids are used for 5 to 15 days, with a dose of 0.25 to 0.5 mg/kg/d prednisone equivalent. Parenteral corticosteroid injections into polyps or nasal turbinates are not recommended. Antibiotic therapy is of minimal value except for occasional exacerbations, since the inflammation is not dependent on bacteria. Computed tomography imaging is often misinterpreted as indicating infection and unnecessary antibiotic therapy is frequently used. Antistaphylococcal therapy, using doxycycline, for eosinophilic NPs may be useful but has not been used specifically in AERD.⁴¹ Leukotriene antagonists are used because of the increased production of LTs, but the clinical response is not always evident.^{42,43} The benefit of LT inhibitors is probably greater for the comorbidity of asthma than for nasal and sinus inflammation. Oral

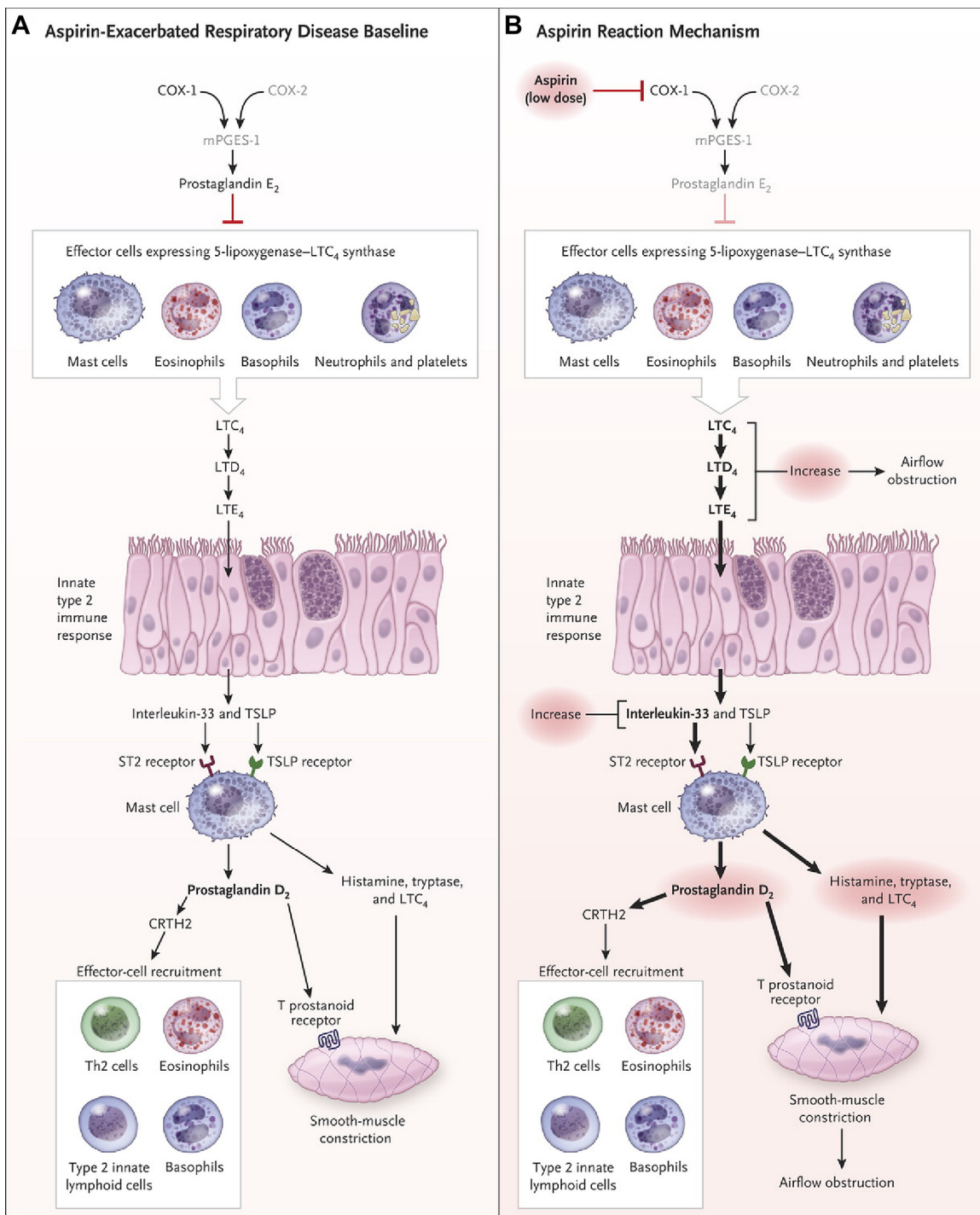


FIGURE 4. Putative mechanisms of AERD driven by a lipid mediator hierarchy. **A**, Insufficient function of the inducible cyclooxygenase (COX)-2—microsomal PgE₂ synthase 1 (mPGES-1)—dependent system of PgE₂ production facilitates persistent synthesis of leukotriene C₄ (LTC₄) by effector cells expressing 5-lipoxygenase—LTC₄ synthase (including LTC₄ synthase—expressing platelets adherent to 5-lipoxygenase—expressing granulocytes). The structural cell—derived cytokines IL-33 and thymic stromal lymphopoietin (TSLP) promote ongoing inflammation and release of mast-cell products, including prostaglandin D₂. **B**, The administration of aspirin or other nonselective NSAIDs depletes the residual PgE₂, permitting strong 5-lipoxygenase activation and further generation of LTC₄. Cysteinyl leukotrienes induce the release of IL-33 and consequent mast-cell activation, with bronchoconstriction occurring as a result of the direct effects of cysteinyl leukotrienes, prostaglandin D₂, and other mast cell—derived products. Prostaglandin D₂ recruits effector cells expressing chemoattractant receptor homologue expressed by T_H2 cells (CRTH2) to the respiratory tissue and induces bronchoconstriction through T prostanoid receptors. *CRTH2*, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *LTD*₄, leukotriene D₄; *ST2*, membrane interleukin-33 receptor. (Reprinted with permission from Laidlaw TM, Boyce JA. Aspirin-exacerbated respiratory disease—new prime suspects. *N Engl J Med* 2016;374:484-8. Copyright 2016 Massachusetts Medical Society).²³

antihistamine therapy, either or topical, is not effective for CRS with NP but has not been studied in AERD with CRS.

Other therapies include aspirin desensitization followed by chronic therapy to reduce nasal and sinus mucosal inflammation, although intolerance due to gastrointestinal bleeding or dyspepsia may limit the tolerance of therapy.^{5,6} The dose is generally 325 to 650 mg of ASA once or twice daily. One double-blind study does not support a benefit with ASA desensitization¹⁵ but others show benefit.^{16,17} Surgical therapy to remove the obstructing nasal polyps and to debulk the sinus mucosal disease is rarely helpful in the long-term but will provide temporary symptom relief. The role of allergen immunotherapy is minimal as most affected subjects are not allergic to inhalants. mAbs against IgE or T_H2 cytokines, such as omalizumab, mepolizumab, or dupilumab, have been tried in a small number of patients, but not specifically in AERD with CRS.⁴⁴⁻⁴⁸

Genetics

Genetic studies are inconclusive, with candidate gene strategies describing various genetic associations that vary in ethnically diverse populations.¹ Most studies have focused on the arachidonic acid pathway, both LT or prostaglandin synthesis and LT receptors, and eosinophil-related genes.^{38,49} Up to 63 genes were studied in a Japanese population with regulatory genes for PgE2 and the PgE2 receptor subtype 3 most associated with AERD.⁵⁰ HLA marker association also has been described, with HLA-DPB*0301 occurring more commonly in AERD with CRS in Korean and Polish populations.⁵¹ Chemoattractant receptor homologous molecule expressed on T_H2 cells (CARTH2), chemokine receptor 3 or eotaxin and eotaxin-2 receptor (CCR3), regulated on activation, normal T cell expressed and secreted or CCL5 (RANTES), and IL-13 variants affect eosinophil biology and genetic differences of these are associated with AERD with CRS. Genome-wide association studies are inconclusive with respect to identifying a primary genetic predisposition for AERD with CRS.⁵²⁻⁵⁴

Biomarkers

Biomarkers include evidence of LT dysregulation and striking mucosal eosinophilia. Urinary quantification of LTE4, the final degradation product of LTs, shows an increase in LT metabolism, which is enhanced by ASA/NSAID ingestion. Nasal lavage analysis after ASA challenge also shows an increase in LTs.³² Nasal and sinus mucosal eosinophilia and lower airway eosinophilia in subjects with asthma is consistently identified along with eosinophilic-related products, such as major basic and eosinophil cationic proteins. In contrast to the increase in urinary LTE4, nasal eosinophilia is shared with allergic rhinitis and eosinophilic rhinosinusitis without AERD, making this observation a less specific biomarker. Mast cell products, such as tryptase, PgD2, and histamine, are increased in nasal lavage of affected subjects and PgD2 degradation products in the urine following ASA/NSAID challenge.³⁶ This supports a role for mast cells in its pathogenesis. The more common condition of allergic rhinitis is also associated with nasal mast cell mediators. Thus, these nasal findings are not a specific biomarker.

DEFINITION

AERD is defined by NP, asthma, and worsening of upper airway complaints and congestion with the ingestion or topical application of ASA/NSAIDs. Historical ASA/NSAID hypersensitivity is clinically used, but compared with double-blind placebo control challenges, overestimations of AERD usually result.^{8,9}

RECOMMENDATION FOR INFORMATION TO BE OBTAINED TO DETERMINE THE ENDOTYPE

The cellular and biochemical phenotype is characterized by an increase in the following: mast cell products, LT production, and various cytokines that generally attract eosinophils. These findings are associated with the clinical phenotype of eosinophilic rhinosinusitis with NPs and worsening of symptoms with ASA/NSAID ingestion or topical application. This clinical description is sufficiently specific to define AERD without demonstrating enhanced baseline LT production that is further increased by ASA ingestion. Defining the endotype will require better understanding of the initial, essential pathogenetic events and identification of genetic and/or environmental factors responsible for the initiation of disease (Figures 1, 3, and 4).

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

Progress will require definitions as to the initial event in the pathogenesis and whether there are subtypes of this disease. The role of infectious disease, particularly viral infection, as an initiator is suggested by clinical histories. Eosinophilia occurs without ASA hypersensitivity and the increase in LT or decrease in PgE2 production presumably precedes the eosinophilic CRS, suggesting that LT or prostaglandin dysregulation is essential for the pathogenesis. Specific questions related to the pathophysiology include the following:

1. What is the initiating event in the CRS and abnormal arachidonic acid metabolism?
2. What determines the development of AERD with CRS versus other T_H2 high, eosinophilic NPs without AERD?
3. Can the persistent increased LT production in AERD with CRS be decreased more than achieved with the leukotriene synthesis inhibitor zileuton and regular NSAID ingestion?
4. Why are leukotriene inhibitor therapies not more effective in AERD with CRS?
5. Is a deficiency of PgE2 the initiating event in AERD with CRS?
6. Why does ASA desensitization followed by daily ingestion improve the mucosal inflammation?
7. What is responsible for the refractory period following a respiratory exacerbation following ASA/NSAID ingestion?
8. Why are symptoms of rhinoconjunctivitis present for years before ASA/NSAIDs hypersensitivity develops?
9. Why do most but not all subjects with AERD have asthma?
10. What is the critical effect of daily ASA/NSAID ingestion that chronically improves the respiratory symptoms?
11. What is the role of staphylococcal infection, specific immune response to *Staphylococcus aureus*, and antibiotic therapy in the development or treatment of AERD with CRS?
12. Are biologic modifiers that affect mast cells or eosinophils effective, long-term therapy for AERD with CRS without asthma?

SUMMARY

CRS with NP and ASA/NSAID sensitivity is a specific phenotype and probable endotype of CRS that is associated with abnormal arachidonic acid metabolism, both a decrease in PgE2 and an increase in LTs. The condition is recognized by the association of eosinophilic CRS and acute worsening of mucosal

inflammation with oral ingestion or topical application of ASA/NSAIDs. Desensitization to ASA/NSAID and chronic therapy likely improves the severity of symptoms. Medical management includes systemic and topical corticosteroids and oral LT modifiers. Biologic therapies, such as omalizumab and mepolizumab, may be helpful but have not been sufficiently studied in this disease.

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