# Pathogenesis of Aspirin-Exacerbated Respiratory Disease and Reactions

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## INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is characterized by the quatrad of asthma, eosinophilic rhinosinusitis, nasal polyposis, and the onset of respiratory reactions after ingestion of aspirin or any other inhibitor of the cyclooxygenase 1 (COX-1) enzyme. Although precipitation of acute reactions by ingestion of COX-1 inhibitors is the defining feature of the syndrome, the underlying inflammatory respiratory disease process begins and continues independently of exposure to aspirin or nonsteroidal antiinflammatory drugs (NSAIDs). The clinical course of the respiratory disease is often stereotypical, which suggests a common underlying cause and mechanism. Typically, the syndrome begins with severe nasal congestion, often after an apparent viral upper respiratory infection in young adulthood, which progresses to chronic eosinophilic rhinosinusitis and recurrent nasal polyposis. During the evolution of the sinus disease, symptoms of lower respiratory tract disease also begin and persistent asthma is diagnosed. The asthma tends to be severe, and individuals with AERD have significantly lower baseline lung function measurements than do those with aspirin-tolerant asthma, suggesting the effects of airway remodeling.[1] If patients with AERD ingest aspirin or an NSAID, an acute reaction develops, characterized by both upper and lower respiratory symptoms. Neither the pathophysiology of the underlying disease nor the mechanisms of the reactions to NSAIDs are entirely understood. Both the baseline respiratory pathology of AERD and the clinical reactions to NSAIDs are accompanied by aberrant metabolism of arachidonic acid, the precursor of both leukotrienes (LTs) and prostaglandins (PGs). This article reviews potential casual mechanisms responsible for the underlying disease, the confirmatory reactions to COX-1-active drugs, and the disturbances and pathogenetic roles of the lipid mediator systems.

## PATHOGENESIS OF THE UNDERLYING RESPIRATORY DISEASE

### Histopathology, Cytokines, and Microbes

Histologically, AERD is characterized by intense inflammation in the upper and lower airways. The numbers of eosinophils identified in the mucosal and submucosal compartments of bronchial and nasal biopsies exceed the numbers found in biopsies from

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aspirin-tolerant asthmatic individuals by 2 to 3-fold.[2,3] Degranulated mast cells are frequent. Lavage fluids obtained from the nasal and bronchial tissues show both higher percentages of eosinophils and higher levels of eosinophil cationic protein, when compared with lavage fluids from aspirin-tolerant controls.[3–5] Thus, even without aspirin provocation, there is evidence for an active, ongoing inflammatory response dominated by eosinophils and mast cells in the respiratory tissue in AERD. This persistent inflammation likely contributes substantially to the recurrent development of severe nasal polyps,[6] with the soluble products of eosinophils and mast cells causing edema and fibroproliferation.[7]

The mechanism by which granulocytes are drawn into the respiratory tissues is not fully understood. In individuals with AERD, aspirin challenges are associated with a significant increase in serum levels of eotaxin-2, a potent and selective chemoattractant for eosinophils.[8] A recent study[9] showed a markedly increased frequency of leukocytes associated with platelets in the nasal polyp specimens of patients with AERD compared with polyps from aspirin-tolerant controls (Fig. 1). Moreover, the percentages of eosinophils, neutrophils, and monocytes with adherent platelets were several-fold higher in the blood of individuals with AERD than in the blood of aspirin-tolerant controls. The platelet-adherent subsets of each leukocyte type expressed higher expression of both $\beta_1$-integrins and $\beta_2$-integrins than did the corresponding nonadherent subset. These findings suggest that a platelet-dependent pathway may facilitate inflammation of the respiratory mucosa in AERD by priming leukocytes for entry into the inflamed tissues. Resident eosinophils in the nasal polyps store interleukin 5 (IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF), both of which are viability sustaining factors for eosinophils.[10] Another study reported that both mast cells and eosinophils staining positively for IL-5, as well as mast cells staining for GM-CSF, were several-fold higher in bronchial biopsies from patients with AERD than from aspirin-tolerant individuals.[11] These studies suggest that resident cells of the innate immune system contribute substantially to generating the cytokines that drive eosinophilic inflammation in a self-perpetuating fashion.

Although the histopathology of AERD supports the importance of effector cells of the allergic response, individuals with AERD frequently lack skin test reactivity to allergens commonly associated with allergic asthma and rhinosinusitis.[1,12] On average, total IgE levels tend to be slightly increased in the serum of patients with AERD compared with nonasthmatic controls, but lower than the levels found in the serum of atopic, aspirin-tolerant individuals[1,13] Some studies have identified higher levels of specific IgE against staphylococcal enterotoxin B in serum[13] and nasal polyps[14] from patients with AERD than from aspirin-tolerant controls. It is unclear whether these findings represent a direct causal relationship to staphylococcal colonization, or whether IgE responses to *Staphylococcus aureus* or its toxins reflect an upstream perturbation of an aberrant immune response to other microbes. Although a microbial pathogenesis has long been suspected in AERD, no consistent microbial isolates (including *Staphylococcus*) have been reported, nor are there geographic patterns suggestive of outbreaks.

## LIPID MEDIATORS IN THE PATHOGENESIS OF AERD

### Cysteinyl LTs

A fundamental characteristic of AERD is striking overproduction of cysteinyl LTs (cysLTs), a class of potent lipid inflammatory mediators derived from arachidonic acid.[15,16] Mast cells, eosinophils, and platelet-adherent leukocytes, all of which abound in the respiratory tissue of patients with AERD, each have the capacity to synthesize $LTC_4$, the parent cysLT, although it is unclear if the overproduction of cysLTs represents a fundamental abnormality or is a consequence of greater numbers and activation of these inflammatory cells. After liberation of arachidonic acid by cytosolic phospholipase $A_2$, arachidonic acid is oxidized by

5-lipoxygenase (LO) to form the unstable intermediate $LTA_4$, which is then conjugated to reduced glutathione by the terminal enzyme $LTC_4$ synthase ($LTC_4S$) to form $LTC_4$. $LTC_4$ is exported from the cell and enzymatically converted into $LTD_4$ and then into the stable end-metabolite $LTE_4$. Baseline urinary $LTE_4$ levels, a marker of systemic cysLT production, are 3 to 5 times higher in patients with AERD than in their aspirin-tolerant counterparts.[15] These levels increase further from the increased baseline (by as much as 10-fold) after challenges with COX-1-active drugs (see later discussion). Baseline levels of $LTE_4$ predict the magnitude of bronchoconstriction occurring during provocative aspirin challenges.[17] The short-lived LT mediators, $LTC_4$ and $LTD_4$, and their stable metabolite $LTE_4$ can all induce edema, bronchoconstriction, and airway mucous secretion.[18–20] In addition, $LTE_4$, the weakest bronchoconstrictor of the 3 cysLTs, induces marked recruitment of eosinophils to the airways in asthmatic patients.[21] Animal models also support a role for cysLTs in driving tissue fibrosis and airway remodeling.[22,23] Thus, cysLTs almost certainly contribute to the chronic inflammation and airway remodeling characteristic of AERD. The pathogenetic importance of the cysLTs in AERD is validated by the efficacy of drugs that interfere with their synthesis or block 1 of their receptors,[24,25] both of which improve disease control and sinonasal function.

There are several potential mechanistic explanations for the overproduction of cysLTs in AERD. Platelets, which express $LTC_4S$, can convert leukocyte-derived $LTA_4$ to $LTC_4$ when they adhere to 5-LO-expressing leukocytes.[26,27] Leukocyte-adherent platelets accounted for most $LTC_4S$ activity among peripheral blood granulocytes isolated from the blood of individuals with AERD, and the levels of urinary $LTE_4$ correlated strongly with the frequencies of platelet-adherent eosinophils, neutrophils, and monocytes.[9] Immunohistochemical studies indicated that eosinophils in bronchial and sinonasal biopsies from individuals with AERD show selective overexpression of $LTC_4S$ protein, but not 5-LO or 5-LO-activating protein.[3] Accordingly, peripheral blood eosinophils from individuals with AERD express more mRNA for *LTC4S* than do eosinophils from aspirin-tolerant controls.[28] A common polymorphic variant of the *LTC4S* allele shows a higher degree of promoter activity than the wild-type allele and was associated with an increased risk of AERD in a Polish population.[28] However, this association was not replicated in a cohort from the United States.[29] The percentages of mast cells and eosinophils in bronchial biopsies from patients with AERD staining positively for 5-LO were several-fold higher than in biopsies from aspirin-tolerant asthmatic controls.[30] Impaired functions of $PGE_2$, a COX pathway product that suppresses the activity of 5-LO (see later discussion), could also contribute to cysLT overproduction in AERD. Thus, overproduction of cysLTs likely relates to factors that both increase the activity of 5-LO and the availability of the substrate $LTA_4$, and increase the availability of the terminal enzyme, $LTC_4S$, including increased granulocyte-adherent platelets and increased $LTC_4S$ expression by eosinophils.

## CysLT Receptors

In addition to overproduction of cysLTs, individuals with AERD also show enhanced end-organ reactivity to the cysLTs. The functions of cysLTs are mediated by at least 2 G protein-coupled receptors (GPCRs), termed $CysLT_1R$ and $CysLT_2R$. The existence of yet-to-be-discovered cysLT receptors (CysLTRs) is likely, based on studies performed in receptor-null mice.[31,32] The high-affinity receptor for $LTD_4$, $CysLT_1R$, is overexpressed in nasal tissue inflammatory cells of patients with AERD compared with aspirin-tolerant controls.[33] The cause of this increased receptor expression is not known, although there are 3 single nucleotide polymorphisms (SNPs) in the promoter region of *CYSLTR1* in which mutant variants have been found to be associated with AERD. The mutant variants showed higher promoter activity, suggesting that these polymorphisms could modulate $CysLT_1R$ expression and lead to increased susceptibility to AERD.[34] Although $CysLT_1R$ has trivial

affinity for $LTE_4$, patients with AERD show a selective hyperresponsiveness to bronchoconstriction induced by inhaled $LTE_4$ compared with aspirin-tolerant asthmatic controls,[35] suggesting that AERD involves additional upregulation of an unidentified $LTE_4$-specific receptor. Polymorphisms in the *CYSLTR2* gene encoding $CysLT_2R$, which negatively regulates the actions of $CysLT_1R$,[36,37] are also associated with AERD, and certain alleles were associated with the magnitude in the decrement in $FEV_1$ (forced expiratory volume in first second of expiration) measured during aspirin provocation.[38] Collectively, these observations suggest that the end-organ reactivity to cysLTs that characterizes AERD may be partly caused by genetically determined patterns of CysLTR expression or function. Moreover, the selective $LTE_4$ hyperresponsiveness in the face of high systemic levels is consistent with a potentially unique role for this stable end-metabolite of cysLTs in driving the disease.

## COX PATHWAY PRODUCTS IN AERD

### Proinflammatory PGs

PGs derive from COX-dependent metabolism of arachidonic acid. The COX-derived precursor, $PGH_2$, is converted to 1 of 5 bioactive terminal products ($PGE_2$, $PGF_2$, $PGI_2$, $PGD_2$, and thromboxane $A_2$ [$TXA_2$]) by corresponding isoform-specific synthases (Fig. 2). These terminal PG synthases show cell-selective expression and in some instances preferential coupling to COX-1, the more aspirin-sensitive COX isoform, or to COX-2, which is more resistant to inhibition by aspirin.[39] Based on their pharmacologic properties, some PGs are candidate pathogenic effectors in AERD. $TXA_2$, the dominant COX product of platelets, which can also be generated by monocytes, mast cells, and granulocytes, is a potent bronchoconstrictor[40] and an inducer of endothelial adhesion molecule expression (intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule).[41] Metabolites of $TXA_2$ are present in higher levels in bronchoalveolar lavage fluid from patients with AERD compared with aspirin-tolerant asthmatics at baseline,[5] potentially reflecting the presence of platelets in the respiratory tissue (see Fig. 1). Furthermore, $TXA_2$ may be involved in the bronchoconstrictive effects of cysLTs, because the increase in airway resistance induced by either $LTC_4$ or $LTD_4$ in guinea pigs is prevented by a selective $TXA_2$ synthase inhibitor.[42] Moreover, the potentiation of histamine reactivity of human and guinea pig bronchi by $LTE_4$ could be blocked by an antagonist of the T prostanoid (TP) receptor, the only high-affinity receptor for $TXA_2$, or by pretreatment of the tissues with indo-methacin to block COX function.[43] Thus, some of the clinical pharmacology of $LTE_4$ may relate to an incompletely explained capacity for this mediator to use $TXA_2$ or TP receptors as effectors. Although immunohistochemical studies of the TP receptor are lacking because of the lack of specific antibodies, there are 2 SNPs of the *TBXA2R* that are associated with AERD in a Korean population.[44]

$PGD_2$ is the dominant COX pathway product of mast cells.[45] Base line levels of $PGD_2$ metabolites are higher in the serum and nasal polyps from patients with AERD than in samples from aspirin-tolerant controls,[46] possibly reflecting the ongoing activation of mast cells in AERD. $PGD_2$ is a bronchoconstrictor,[47] presumably through the effects of its stable metabolite, 9 ,11 -$PGF_2$, acting at TP receptors.[48] $PGD_2$, acting through the CRTH2 receptor, is also a potent chemoattractant for eosinophils.[49] The persistent production of $PGD_2$ in the inflamed respiratory tissues of patients with AERD may therefore contribute to the ongoing airway dysfunction and eosinophilic inflammation characteristic of the phenotype. Whereas metabolites of $TXA_2$ usually decrease in response to aspirin challenge in AERD,[50] $PGD_2$ metabolites in the bronchoalveolar lavage fluid or urine do not (and even increase in some studies),[46,51] suggesting that these COX-derived effectors either derive principally from separate cell types (platelets and mast cells, respectively), or are generated through different COX isoforms in AERD. In that regard, it is noteworthy that COX-2

protein is expressed more strongly by mast cells in bronchial biopsies from patients with AERD than by mast cells in biopsies from aspirin-tolerant controls,[52] suggesting a potential explanation for aspirin-resistant $PGD_2$ production in this disease.

### Antiinflammatory PGs

$PGE_2$ may be the most essential PG for maintaining homeostasis of inflammatory responses in the airway in general and in AERD in particular. Of all COX products, $PGE_2$ is unique for its bronchoprotective and antiinflammatory effects in the airway. $PGE_2$ blocks allergen-induced early-phase and late-phase responses in atopic asthmatics[53] and blocks mast cell activation through a pathway dependent on 1 of its 4 GPCRs, termed the E prostanoid 2 ($EP_2$) receptor, and its downstream effectors, adenylate cyclase and cyclic adenosine monophosphate.[54,55] $PGE_2$ also uses the same signaling mechanism to induce phosphorylation and prevent translocation of 5-LO to the nuclear envelope[56] and can thus control the generation of cysLTs, a function that may be especially relevant to AERD. The importance of this potential mechanism is supported by the fact that inhaled $PGE_2$ prevents both the airway obstruction and the increase in urinary $LTE_4$ occurring in response to aspirin challenge in patients with AERD.[57] $PGE_2$ also potently inhibits eosinophil migration,[58] and both endogenous and exogenous $PGE_2$ suppress allergen-induced pulmonary eosinophil accumulation in humans[53] and rodents.[59] $PGE_2$ signals through $EP_2$ receptors to dampen the proliferation of fibroblasts and their production of collagen.[60] Collectively, these observations suggest that deficient $PGE_2$ generation or $EP_2$ receptor function on both hematopoietic and structural cells could also be relevant to the pathogenesis of AERD.

$PGE_2$ is generated primarily by COX-2 and a partner terminal synthetic enzyme, microsomal $PGE_2$ synthase 1 (mPGES-1). These 2 enzymes are coexpressed by epithelial cells, fibroblasts, and macrophages and are frequently upregulated in tandem during inflammatory responses.[61] There is substantial evidence that $PGE_2$ production and the functions of COX-2/mPGES-1 are impaired in the respiratory tissues in AERD. Although urinary levels of $PGE_2$ metabolites in AERD are similar to those in aspirin-tolerant controls, nasal polyps from patients with AERD contain markedly lower levels of $PGE_2$ than do sinonasal tissues from aspirin-tolerant individuals.[62] These levels are inversely related to the levels of cysLTs recovered from the same polyps. Peripheral blood leukocytes isolated from patients with AERD produce less $PGE_2$ than aspirin-tolerant controls,[63] and both nasal epithelial cells and cultured fibroblasts from nasal polyps of patients with AERD generate less $PGE_2$ in vitro than do cells from aspirin-tolerant asthmatic controls.[64,65] The expression of COX-2 mRNA is diminished in nasal polyps from patients with AERD compared with that in normal nasal mucosa and in polyps from aspirin-tolerant patients,[66] and the IL-1 - induced upregulation of COX-2 mRNA and protein expression in cultured fibroblasts from nasal polyps of patients with AERD is markedly blunted compared with their upregulation in cells from aspirin-tolerant controls.[65] Although there are no studies reporting the expression of mPGES-1 in AERD, the *PTGES* gene encoding this enzyme is hypermethylated (a mechanism for gene silencing) in nasal polyps from patients with AERD.[67] Collectively, these studies support defective function of the major system responsible for maintaining local $PGE_2$ in inflammation, potentially mediated by epigenetic mechanisms. A predicted outcome of the failure to appropriately upregulate COX-2 and mPGES-1 expression in the respiratory tissue is a dependency on COX-1 to provide the residual $PGE_2$ needed to maintain homeostasis of eosinophilic inflammation, mast cell activation, and 5-LO pathway activity. As noted later, this hypothetical dependency on COX-1 could contribute to a state of aspirin sensitivity.

### Alterations in $EP_2$ Receptor Expression and Function in AERD

Given the $EP_2$ receptor-dependent actions of $PGE_2$ noted earlier, it is noteworthy that the percentages of neutrophils, mast cells, eosinophils, and T cells expressing the $EP_2$ receptor are lower in nasal mucosa biopsies from patients with AERD compared with those in biopsies from aspirin-tolerant asthmatic controls.[68] Similar findings were recently reported for bronchial biopsies.[69] In addition, cultured fibroblasts from the nasal polyps of patients with AERD display decreased induction of the $EP_2$ receptor protein by IL-1 compared with fibroblasts from aspirin-tolerant patients.[65] Several SNPs in the promoter region of the $EP_2$ gene have been found to be associated with AERD, and the most significantly associated SNP, uS5, is located in the regulatory region of the $EP_2$ gene in a signal transducer and activator of transcription-binding consensus sequence and it confers reduced transcription activity.[70] However, this regulatory SNP was identified in only ~30% of patients with AERD versus ~20% of controls. The expression of $EP_2$ receptors (as well as that of COX-2) can become dysregulated by epigenetic mechanisms in cancer[71,72] and in pulmonary fibrosis.[73,74] It seems plausible that similar epigenetic mechanisms may promote deficiencies in these same targets in AERD, even in individuals who do not possess SNPs that dysregulate their expression.

### Other Arachidonic Acid Metabolites in AERD

Lipoxins (LXs) are unstable antiinflammatory derivatives of arachidonic acid, synthesized through transcellular mechanisms involving cooperation between 5-LO and platelet 12-LO[75] or 5-LO and epithelial cell-derived 15-LO.[76] In the presence of aspirin, COX-2 can function as a 15-LO and convert leukocyte-derived $LTA_4$ to 15-epi-$LXA_4$, also known as aspirin-triggered LX.[77] LXs inhibit cysLT production and eosinophilic infiltration of pulmonary tissue in rodent models of pulmonary inflammation,[78] and in vitro studies suggest that they are high-affinity antagonists of $CysLT_1R$.[79] Calcium ionophore stimulation of peripheral blood leukocytes from patients with AERD results in the release of less $LXA_4$ than does stimulation of leukocytes from the blood of aspirin-tolerant asthmatic control individuals.[80] Given the predicted antiinflammatory function of $LXA_4$, a deficient capacity to generate this mediator could contribute to the dysregulated inflammatory responses and cysLT-driven pathobiology of AERD, although this has not been validated in vivo.

# CROSS-TALK BETWEEN ARACHIDONIC ACID PATHWAYS IN THE PATHOBIOLOGY OF AERD AND GENESIS OF ASPIRIN-INDUCED REACTIONS

Although the events that initiate the development of AERD are unknown, the complex set of disturbances in the homeostasis of inflammation and lipid mediator production that characterize the basal state of the disease may hinge on a deficient synthesis of $PGE_2$ or on a diminished ability for it to signal through $EP_2$ receptors (Fig. 3). First, lowered levels of $PGE_2$ in the tissues combined with diminished expression of $EP_2$ receptors on the respiratory tissue granulocytes would allow for the dramatically elevated levels of cysLTs found in patients with AERD: it would permit enhanced $LTC_4$ synthesis by eosinophils and mast cells and would increase the neutrophil-derived $LTA_4$ available for conversion to $LTC_4$ by adherent platelets. Second, deficiencies in available $PGE_2$ and $EP_2$ receptor function would promote ongoing activation of mast cells and would remove a check on the chemotaxis of eosinophils. Third, $EP_2$ receptor signaling maintains TP receptors in a relative state of phosphorylation/desensitization via protein kinase A, and a recent study[59] revealed that $EP_2$ receptor signaling and mPGES-1-derived $PGE_2$ were essential to prevent exaggerated TP receptor-driven upregulation of endothelial cell ICAM-1 and consequent allergen-induced pulmonary eosinophilia and airway hyperreactivity. Last, deficient $EP_2$

receptor function on fibroblasts would impair the capacity of local $PGE_2$ to maintain a check on proliferation and collagen production. Thus, baseline impairment of local $PGE_2$ generation and $EP_2$ receptor signaling would likely promote persistent inflammation and ongoing tissue remodeling by several complementary mechanisms in AERD.

The defining respiratory reactions of AERD occur exclusively with drugs that inhibit COX isoforms nonselectively. At the low doses required to cause reactions in AERD, aspirin selectively inhibits the COX-1 isoenzyme[81] and it is inhibition of COX-1, but not of COX-2, which precipitates reactions.[82–85] All COX-1 inhibitors induce stereotypically similar respiratory reactions in patients with AERD, indicating that the ability of these structurally diverse drugs to inhibit COX-1 per se is via their pharmacologic actions. Although the basal state of AERD does not require exposure to COX inhibitors, the remarkable ability for low doses of aspirin (or any COX-1-active NSAID) to induce reactions implies that the aspirin sensitivity of AERD is caused by a tenuous dependency on COX-1 products to maintain homeostasis. Based on several lines of evidence, COX-1-derived $PGE_2$ is likely relevant to the pathophysiology of reactions to COX inhibitors. Although challenges with aspirin do not deplete $PGE_2$ metabolites in the urine of patients with AERD,[86] this measurement may be more reflective of ongoing renal tubular generation of $PGE_2$ than of that from the respiratory tract. The markedly reduced expression of COX-2 by nasal polyp tissues from patients with AERD implies that the small, residual amounts of local $PGE_2$ are generated primarily through COX-1. Indeed, local concentrations of $PGE_2$ do decrease in nasal lavage fluid after oral aspirin challenges in patients with AERD.[87] It seems likely that the additional low expression of $EP_2$ receptors would magnify the physiologic effects of small changes in local $PGE_2$ levels. In this scenario, depletion of residual $PGE_2$ from the respiratory tract would permit increased activity of 5-LO and a surge of cysLT production and mast cell activation (as shown, respectively, by the characteristic increase in urinary $LTE_4$ and increases in both serum tryptase and $PGD_2$ metabolites occurring after challenge). The observation that inhalation of $PGE_2$ can block both airway obstruction and the increase in urinary $LTE_4$ occurring in response to aspirin challenge further supports a key causative function for depletion of $PGE_2$ in the pathogenesis of reactions to COX-1 inhibitors.[57]

Although COX-1-derived $PGE_2$ may be the major PG responsible for controlling the activity of 5-LO, other COX-1-derived PGs may also play a role in regulating cysLT production during reactions in AERD. $TXA_2$ is largely COX-1-dependent, and urinary levels of its stable metabolite (11-dihidro $TXB_2$) decrease during reactions to aspirin in patients with AERD.[5] As noted earlier, $TXA_2$ may mediate certain $LTE_4$-dependent physiologic events, and this property may account for the rapid loss of selective $LTE_4$ hyperresponsiveness observed after desensitization to aspirin.[88] However, $TXA_2$ in platelets also suppresses the activity of $LTC_4S$, presumably through an auto-crine, TP receptor-dependent pathway that maintains phosphorylation of $LTC_4S$ by protein kinase C.[89] Treatment of platelets ex vivo with aspirin rapidly removes this suppression and potentiates the activity of $LTC_4S$. It is thus possible that simultaneous depletion of $PGE_2/EP_2$ signaling on leukocytes and $TXA_2/$ TP signaling on platelets by aspirin could further dysregulate cysLT generation, especially from platelet-leukocyte complexes.

Given the ability of the 5-LO inhibitor zileuton and antagonists of $CysLT_1R$ to blunt the clinical and physiologic features of reactions to COX-1 inhibitors, 5-LO pathway products in general and cysLTs in particular are unequivocal effectors of reactions. Nevertheless, neither the cellular sources of these mediators during reactions nor the targets of their effects in reactions are completely understood. Both mast cells and eosinophils possess the complete repertoire of enzymes needed to generate cysLTs from endogenous arachidonic acid. As noted earlier, soluble markers of both eosinophil and mast cell activation increase in the lavage fluids, serum, or urine of patients with AERD with aspirin or lysine aspirin

challenges. Thus, both cell types are likely to contribute to the surge in cysLTs that typify reactions. Inhalation of the mast cell-stabilizing drugs cromolyn or nedocromyl block aspirin-induced bronchoconstriction, further supporting the role of mast cell activation (and likely mast cell-derived cysLTs) in the reactions to aspirin.[90,91] Receptors for cysLTs are broadly expressed by both structural and hematopoietic cells, and immunohistochemical studies indicate that the expression of $CysLT_1R$ by respiratory tract eosinophils and mast cells is upregulated in AERD.[33] The administration of zileuton to subjects with AERD not only dramatically reduces the nasal symptoms of reactions to lysine aspirin challenge, but markedly reduces the concentrations of mast cell tryptase recovered from the nasal lavage fluid compared with the levels found in fluids from placebo-treated challenged controls.[24] It is thus likely that cysLTs induce a diverse array of physiologic effects during reactions beyond $CysLT_1R$-dependent bronchoconstriction. The fact that $LTE_4$, the most abundant mediator detected during reactions, acts by receptors other than $CysLT_1R$ and $CysLT_2R$ makes this hypothesis a virtual certainty Fig. 2.

## SUMMARY

Physiologic and pharmacologic studies in humans strongly support the hypothesis that AERD involves fundamental disturbances in both the production of and endorgan responsiveness to eicosanoids that are regulators of homeostasis ($PGE_2$) and those that are effectors (cysLTs). The likelihood that these disturbances are acquired in adulthood implies potential epigenetic modifications of the relevant mediator systems as a result of only partially clarified environmental factors (eg, potentially viral or bacterial infections, inhaled pollutants). The rapid development of technology permitting analyses of the epigenetic landscape and the microbiome may permit finer detailing of the evasive causal agents and lesions. Meanwhile, the putative pathobiological mechanisms of AERD introduce substantial opportunities for targeted therapeutic intervention. The advent of anti-IL-5,[92] tyrosine kinase inhibitors,[93] and antiplatelet drugs[94] for other indications may permit novel therapeutic approaches to AERD by targeting some of the key cellular effectors (eosinophils, mast cells, platelets). Existing or new drugs that act by targeting of candidate mediators and receptors, such as $PGD_2/DP_2$[95] and $TXA_2/TP$,[96] should permit finer detail of their specific roles in disease pathogenesis, as well as providing additional potential efficacy of treatment. The anticipated identification of $LTE_4$-selective receptors and the development of $EP_2$ receptor-selective agonists have substantial therapeutic potential in AERD.

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## KEY POINTS

- Pathogenesis of aspirin-exacerbated respiratory disease (AERD) involves a consistent pattern of aberrant leukotriene generation.

- AERD is associated with deregulated expression and function of enzymes and receptors responsible for the production and function of lipid mediators that are protective against reactions to cyclooxygenase inhibitors.

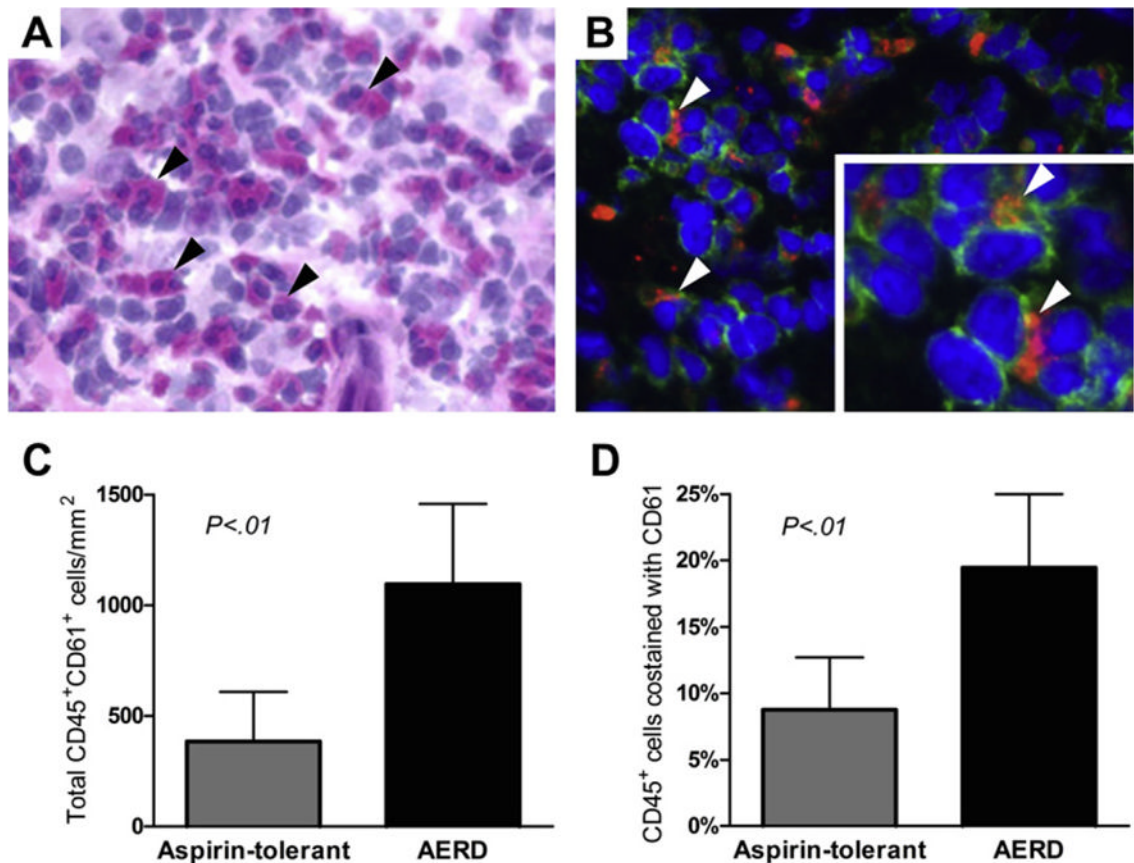- AERD is acquired rather than hereditary.

**Fig. 1.**
Detection of platelet-leukocyte aggregates in nasal polyp tissue. (*A*) Hematoxylin-eosin staining of nasal polyp tissue from a patient with AERD shows many eosinophils (*black arrowheads*) and (*B*) immunofluorescent staining of the same tissue shows leukocytes (*green*, CD45$^+$) with adherent platelets (*red*, CD61$^+$) (*white arrowheads*). Photographs are shown at 400× magnification. (*C*) Total numbers of CD45$^+$cells that colocalized with CD61 and (*D*) percentages of CD45$^+$ cells that colocalized with CD61 in the nasal polyp tissue from aspirin-tolerant controls with sinusitis (n = 4) and patients with AERD (n = 6). Data are expressed as mean + standard deviation. (*Data from* Laidlaw TM, Kidder MS, Bhattacharyya N, et al. Cysteinyl leukotriene overproduction in aspirin-exacerbated respiratory disease is driven by platelet-adherent leukocytes. Blood 2012;119:3790–98.)
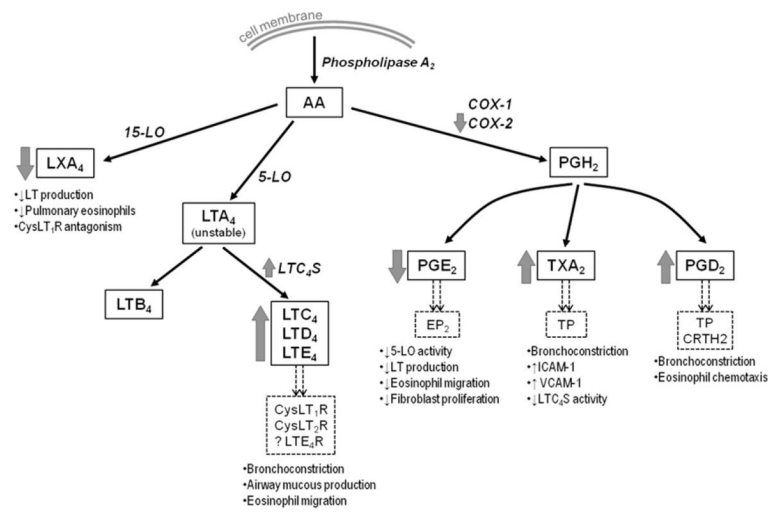
**Fig. 2.**
Metabolism of arachidonic acid. Pathways of arachidonic acid metabolism involved in the pathogenesis of AERD. Enzymes are in italics, relevant receptors are in dashed boxes, and consequences of signaling through each receptor are in bulleted lists. Thick gray arrows show whether expression and function of each enzyme or product are increased or decreased in patients with AERD.
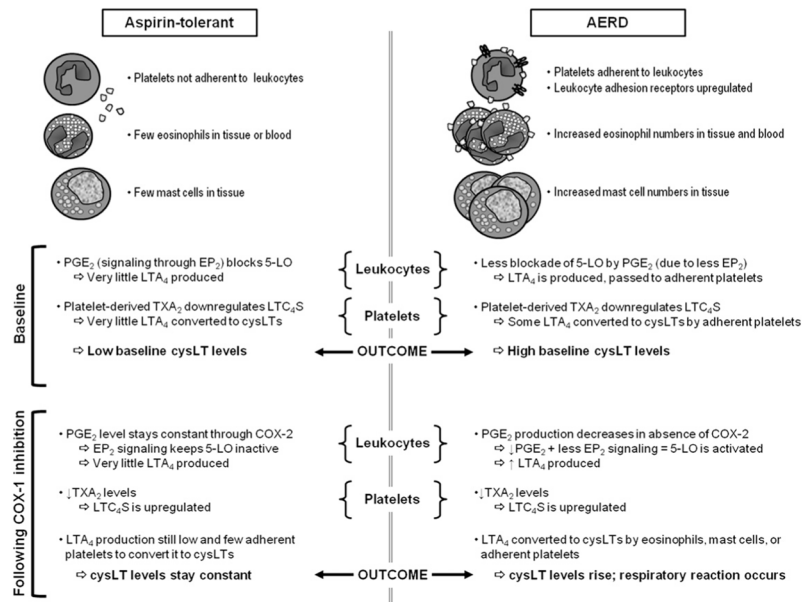
**Fig. 3.**
Summary of the pathogenesis of AERD at baseline and after COX-1 inhibition. Normal mechanisms for the maintenance of homeostasis at baseline and after COX-1 inhibition in aspirin-tolerant control patients are presented on the left. The consequences of abnormalities that lead to both the underlying respiratory disease and the development of reactions on ingestion of COX-1 inhibitors in patients with AERD are presented on the right.