

Aspirin Sensitivity and Desensitization for Asthma and Sinusitis

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NSAIDs—including aspirin (ASA)—that inhibit cyclooxygenase (COX)-1 induce nonallergic hypersensitivity reactions consisting of attacks of rhinitis and asthma. Such reactions occur exclusively in a subset of asthmatic patients who also have underlying nasal polyps and chronic hyperplastic eosinophilic sinusitis. We now refer to their underlying inflammatory disease of the entire respiratory tract as *aspirin-exacerbated respiratory disease*. This review focuses on descriptions of these patients; methods available to diagnose ASA-exacerbated respiratory disease; the unique ability of all NSAIDs that inhibit COX-1 to cross-react with ASA; lack of cross-reactivity with selective COX-2 inhibitors; an update on pathogenesis; and current thoughts about treatment, including ASA desensitization and daily ingestion of ASA itself.

Introduction

In 1922, Widal et al. [1] first described the association of asthma and nasal polyposis in patients who experienced respiratory reactions after ingesting aspirin (ASA). They also conducted the first ASA challenges and ASA desensitization [1]. Their article, published in French, was then ignored for the next 45 years. In 1968, Samter and Beers [2] redescribed the disease that later became known as *Samter's triad* (asthma, nasal polyps, and ASA reactions). We now include chronic hyperplastic eosinophilic sinusitis as a fourth hallmark of the disease, with the preferred name now being *aspirin-exacerbated respiratory disease* (AERD) [3]. The most recent consensus nomenclature describing ASA-induced respiratory reactions is *nonallergic hypersensitivity reactions* [4].

Natural History and Clinical Presentation of AERD

AERD is an acquired disease with an onset of symptoms starting between the teenage years and age 60 [5••]. The average age at onset of symptoms (usually persistent nasal congestion) was 34 and 29 years in two large studies involving 300 and 500 AERD patients, respectively [6,7]. AERD is more prevalent among women than men, and family incidence is quite low (1% to 5%) [6,7].

AERD can appear in individuals who already have allergic rhinitis, asthma, or any other provoking factor (eg, gastroesophageal reflux disease) or can appear *de novo*. In a series of 300 AERD patients referred for ASA desensitization, 64% had positive prick or intradermal wheal and flare skin tests to common environmental allergens, and most had allergic respiratory tract disease before becoming sensitive to ASA and NSAIDs [6]. However, having allergic respiratory disease was not a prerequisite for acquiring AERD, as more than one third of 300 patients never had IgE-mediated respiratory disease.

The first clinical manifestation of AERD is usually nasal congestion, followed by anosmia. In fact, normal olfaction correlates with not having AERD [3]. The original chronic rhinitis progresses to chronic hyperplastic eosinophilic sinusitis with nasal polyposis. In this series of 300 AERD patients, CT or plain radiographs of the sinuses revealed complete opacifications in 94% of patients and mucoperiosteal thickening in 6% [6]. Thus, as with normal smell, normal sinus radiographs predict that a patient will not have AERD.

Rhinitis, sinusitis, and nasal polyps are usually joined by onset or increase in asthma. ASA-/NSAID-induced hypersensitivity reactions can appear at any time in the disease course, but until such an event occurs, an AERD diagnosis cannot be considered. Despite avoidance of ASA and NSAIDs, mucosal inflammation of the upper and lower respiratory tracts persists and progresses. This strongly supports the fact that ingestion of ASA and the older NSAIDs exacerbates an ongoing inflammatory disease rather than causes the disease in the first place [5••].

Prevalence

The prevalence of AERD is difficult to establish. Many patients have the disease but do not know it because they

have not ingested ASA or other NSAIDs. Alternatively, others may experience mild or late asthma attacks after ingesting NSAIDs and cannot correlate drug ingestion with an associated asthma attack or do not know that ASA/NSAIDs can cause asthma attacks.

To circumvent the problem of poor recognition or prior nonexposure to ASA/NSAIDs, investigators have performed prospective oral ASA challenges on various populations of asthmatic patients. In a meta-analysis of 15 studies performed after 1990 using oral aspirin challenges (OACs) to detect ASA hypersensitivity in asthmatic populations, the combined prevalence of AERD was 21% (95% CI, 14% to 29%), whereas in five studies in children (0–18 years of age), the combined prevalence was only 5% (95% CI, 0% to 14%) [8].

When target populations of asthmatics were further stratified and only those who had nasal polyps and abnormal sinus x-rays/CT scans were included, the prevalence of ASA hypersensitivity—discovered by prospective OACs—was found to be even higher (30% to 42%) [9–11].

Respiratory Reactions to ASA and NSAIDs

Cross-reactions among NSAIDs that inhibit cyclooxygenase-1

Patients with AERD react to ASA and all NSAIDs that preferentially inhibit cyclooxygenase (COX)-1, inducing a spectrum of respiratory reactions, including rhinorrhea, nasal congestion, ocular itching and tearing, laryngeal spasm, and asthma attacks [12]. The reactions usually occur within 30 to 60 minutes after ingesting full therapeutic doses of ASA or another NSAID. Assuming that the NSAID doses are in the upper therapeutic range, cross-reactivity among NSAIDs that inhibit COX-1 is 100% (Table 1).

Partial cross-reactivity with poor inhibitors of COX-1

Salsalate and acetaminophen are poor COX-1 inhibitors. However, at higher doses, both can induce mild respiratory reactions in patients with AERD (Table 1). Most patients can safely tolerate up to 650 mg of acetaminophen. However, after ingesting 1000 mg of acetaminophen, 28% experienced mild asthmatic reactions, and another 6% reacted when a dose of 1500 mg was administered [13]. Salsalate can be given safely in doses less than 2000 mg in patients with AERD [14]. However, 2000 mg or more induced mild respiratory reactions in 10% of AERD patients undergoing oral challenges with salsalate.

Partial cross-reactivity with partially selective COX-2 inhibitors

Meloxicam and nimesulide are two anti-inflammatory drugs that preferentially inhibit COX-2 at lower concentrations but can also inhibit COX-1 at higher therapeutic concentrations [15]. Similar to salsalate and acetaminophen, in AERD patients, mild respiratory reactions can occur in a minority of patients (Table 1) [16].

Table 1. Four classes of NSAIDs based on their pharmacologic function

1. Strong COX-1 inhibitors (universal cross-reactions between these NSAIDs occur [at high concentrations, they are COX-2 inhibitors])

Piroxicam
Indomethacin
Sulindac
Tolmetin
Ibuprofen
Naproxen
Naproxen sodium
Fenoprofen
Oxaprozin
Mefenamic acid
Flurbiprofen
Difluinisal
Ketoprofen
Diclofenac
Ketorolac
Etodolac
Nabumetone
Acetylsalicylic acid

2. NSAIDs that inhibit COX-1 poorly (minimally inhibit COX-1 without inhibiting COX-2 at high concentrations)

Acetaminophen (paracetamol)
Salsalate

3. NSAIDs that preferentially inhibit COX-2 but partially inhibit COX-1 when higher doses are given

Nimesulide
Meloxicam

4. Selective COX-2 inhibitors (preferentially inhibit COX-2 but do not inhibit COX-1 at prescribed doses)

Celecoxib*
Rofecoxib†
Valdecoxib†
Etoricoxib†
Parecoxib†
Lumiracoxib†

*Available worldwide.

†Removed from the world market in 2004–2005.

*Available outside the United States.

COX—cyclooxygenase.

Lack of cross-reactivity with selective COX-2 inhibitors

Selective COX-2 inhibitors such as rofecoxib, celecoxib, valdecoxib, etoricoxib, parecoxib, and lumiracoxib are the most recent category of NSAIDs to enter the market (and, in the cases of rofecoxib and valdecoxib, to then exit the

Table 2. Oral aspirin challenges in patients with suspected aspirin-exacerbated respiratory disease

Time	Day 1*	Day 2 (or 1)	Day 3 (or 2)
8:00 AM	Placebo	20–40 mg [†]	100–160 mg
11:00 AM	Placebo	40–60 mg	160–325 mg
2:00 PM	Placebo	60–100 mg	325 mg [‡]
1. Measure FEV ₁ every hour and wait 3 hours between doses			
2. FEV ₁ should be at least 1.5 L to proceed, but < 70% of predicted is preferred			
3. Reactions can be as follows:			
a. Naso-ocular alone			
b. Naso-ocular and a $\geq$ 15% decline in FEV ₁ (classic reaction)			
c. Lower respiratory reaction only (FEV ₁ declines by > 20%)			
d. Laryngospasm with or without a, b, or c (flat or notched inspiratory curve)			
e. Systemic reaction: hives, flushing, gastric pain, hypotension			
4. Aspirin desensitization			
a. After a reaction has been treated and FEV ₁ values have returned to baseline			
b. Repeat the aspirin-provoking dose			
c. If no reaction, continue to escalate the doses as above			
d. At 325 mg aspirin, desensitization is always completed			
e. Give 650 mg as first dose, then treat with 650 mg twice daily			
*A placebo challenge can be conducted the week before. If the patient's baseline FEV ₁ is the same as the previous best value and he or she has not used an albuterol rescue inhaler in the past week, you can skip the 1 day of placebo challenge.			
[†] Using a pill cutter, an 81-mg aspirin tablet can be cut in half or into quarters.			
[‡] If the patient has not reacted to 325 mg, he or she will not react to 650 mg. Therefore, stop after 325 mg and call it a negative challenge.			
FEV ₁ —forced expiratory volume in 1 second.			

market). Celecoxib is the only remaining selective COX-2 inhibitor available in the United States. Many clinicians are apprehensive about prescribing selective COX-2 inhibitors to patients with AERD because warning labels on all coxibs list AERD as a contraindication for prescribing COX-2 inhibitors. However, well-designed single- and double-blind challenge studies have demonstrated that selective COX-2 inhibitors given in therapeutic doses do not cross-react with ASA or other NSAIDs in patients with AERD [17–20]. These facts should not be surprising because the molecular design of COX-2 inhibitors includes a side arm that prevents these molecules from entering the smaller COX-1 channel. Competitive inhibition of COX-1 occurs when NSAIDs fill the COX-1 channel or when ASA acetylates the enzyme. In fact, no scientific evidence supports the US Food and Drug Administration and manufacturer label warnings that cross-reactivity between COX-1 inhibitors and COX-2 inhibitors has ever occurred. The few case reports of COX-2 inhibitors causing reactions have been unrelated to cross-reactivity and are likely IgE recognition of individual COX-2 inhibitors [21] or unknown mechanisms. Celecoxib was also reported to cause asthmatic reactions at very low doses in one AERD patient through unknown mechanisms [22]. In fact, all coxibs have been shown to induce urticarial and anaphylactic reactions [23]. As prescribing physicians, we can never guarantee that a rare reaction to a selective COX-2 inhibitor will not occur, even if the reaction has

nothing to do with COX-1 inhibition. Therefore, standard of care is to give the first full dose of a COX-2 inhibitor in the physician's office to patients with AERD or to asthmatics with unknown sensitivities.

Diagnosis of AERD

The diagnosis of AERD can be definitively established only through provocative ASA or NSAID challenges [3]. There are three types of provocation challenges, depending on the route of administration and challenge drug: oral [3,24], inhalation [25], and nasal [26,27].

OACs are available in the United States. Details on conducting these challenges can be found in Table 2. By cutting 81-mg ASA tablets into quarters, one can start with 20.25 mg and advance doses as per Table 2. Patients are instructed to continue oral and topical corticosteroids, long-acting bronchodilators, leukotriene (LT) modifiers, and systemic corticosteroids because discontinuing these medications may lead to hyperirritable airways. Some medications should be discontinued 24 hours before challenge, including antihistamines and short-acting inhaled β agonists or anticholinergics. LT-modifier drugs do not prevent upper airway reactions but do block or modify bronchospastic reactions during OACs [28,29]. In the United States, a new diagnostic test for nasal challenge—using a dilute solution of ketorolac—recently completed diagnostic trials [30]. Ketorolac solutions (8 mg/mL),

delivered as a nasal spray in increasing doses every 30 minutes, offer an alternative to ASA-lysine nasal challenge, as ASA-lysine has not been approved for use in humans by the US Food and Drug Administration.

Accuracy of the history of a prior reaction to ASA/NSAIDs in predicting positive OACs

In a group of 243 patients referred to us for ASA desensitization, 5 of 12 (42%) of those who had asthma, nasal polyps, and pan sinusitis but no prior exposure to ASA/NSAIDs had positive OACs. If prior exposures to ASA/NSAIDs were associated with asthmatic reactions, positive OACs occurred in 198 of 231 (86%). With two or more prior historical reactions to ASA/NSAIDs, these same patients experienced positive OACs 89% of the time, compared with 80% for single prior reactors ($P = 0.04$). If prior NSAID-associated reactions were so severe that the patient was admitted to an intensive care unit (ICU), OACs were positive in all 45 patients [10]. This large study makes it clear that life-threatening reactions to full doses of ASA usually can be diagnosed by history alone. It further emphasizes how dangerous full therapeutic doses of NSAIDs can be to some patients with AERD but also how ASA/NSAID association histories can be inaccurate with respect to diagnosing AERD when the reactions are less severe.

Inpatient versus outpatient OACs

Controversy exists as to whether it is safe (due to possible severe OAC-induced asthma) to conduct OACs in the ICU, general clinic research center (GCRC), stepdown unit, emergency department holding area, outpatient offices attached to hospitals, offices next to the hospital, or remote offices. If a severe asthma attack occurred during OAC, it seems reasonable to assume that an ICU would be the best place to stop the asthma and support the airways via intubation and ventilation. However, the following questions need to be answered: How often does OAC induce asthma severe enough to require intubation and ventilation? Does a 30% to 50% fall in forced expiratory volume in 1 second (FEV_1) require an ICU facility to render successful treatment? If competent ICU or emergency department nurses were moved to an outpatient department facility and trained and experienced in conducting an OAC, would that be equivalent to or better than conducting an OAC in an ICU with a new nurse every shift? Furthermore, does the risk justify the cost and scheduling difficulties of using an ICU for an OAC?

Each allergy specialist needs to assess the availability of space, resources, and personnel in his or her own office or institution so that an ASA challenge followed by desensitization can be accomplished safely. Unrelated to space and logistics, the following is a perspective on the issue of safety during OAC. At Scripps Clinic, because of early research projects, we started using the GCRC for OACs in 1979. Over the next decade, two patients had asthma attacks induced by OAC that were severe enough that our

judgment was to transport them to the ICU for potential intubation and ventilation. Both continued to receive inhaled bronchodilators in the ICU, and neither required intubation. Both were transported back to the GCRC, and ASA desensitization was completed. Retrospectively, neither required an ICU because the same treatment was rendered in the GCRC by nurses trained and dedicated to conducting OACs. Since 1999, when zileuton, montelukast, and zafirlukast became available for pretreatment, OAC-induced asthma has never been severe enough in any of our patients to consider ICU or intubation. In February 2005, we moved the program to outpatient offices within the hospital building, and in October 2006, we moved to outpatient space in a large clinic building six miles from our hospital. Thus, in more than 1375 OACs, we have never had to intubate a patient after an OAC-induced asthma attack, and no patient has died during OACs.

In our recent study of 210 AERD patients undergoing OAC, we compared the severity of their prior historical reactions to ASA/NSAIDs with the degree of asthma induced by OAC [31]. The results demonstrated no correlation between the historical ASA-/NSAID-induced asthma attack and that induced during graded OAC as measured by decreases in FEV_1 values. Thus, a historical severe asthmatic attack to full doses of ASA/NSAIDs was not predictive of the same events occurring during controlled OAC. This study countered the argument that in these special “high-risk” patients, a severe historical ASA-/NSAID-induced asthma attack required an ICU for OAC. The authors also emphasized the substantial differences between a historical asthma attack, in which the minimum ASA (NSAID equivalent) dose was 325 mg (average, 550 mg), and the OAC challenge, in which the minimum provoking dose in our studies was 30 mg (average, 60 mg of ASA). More important than the place in which OACs are conducted are the experience of the physicians, presence of dedicated and experienced nurses, acceptance of patients whose asthma is under control, continuation of inhaled and/or systemic corticosteroids, and pretreatment with an LT-receptor antagonist.

Pathogenesis

Underlying respiratory disease

The pathophysiology of AERD has only been partially elucidated. In 1988, Szczeklik [32] presented his theory that a viral respiratory infection may be an inciting event that starts the inflammatory cascade that leads to respiratory inflammation and AERD in genetically susceptible individuals. Indeed, many patients remember a “virus cold” at the beginning of their AERD. Recent investigations have identified rhinovirus in the bronchial mucosa of 9 of 14 (64%) patients with chronic asthma but also in bronchial biopsies of two of six (33%) normal controls. In a recent study, in vitro coculture of dendritic cells (or macrophages) and T cells with parainfluenza, respiratory syncytial virus, or rhinovirus produced a brisk prolif-

eration of CD3⁺ and CDR4⁺ cells and release of cytokines that attract eosinophils [33•]. Thus, under the right circumstances, viruses can stimulate not only a neutrophilic response but also an eosinophilic response independent of IgE mechanisms. Is a defect in AERD patients their inability to clear viruses that are surviving in epithelial or inflammatory cells? Do viruses interfere with synthesis of cytokines or T-regulatory cells that under normal circumstances would shut down inflammation in the respiratory mucosa, or do they encourage synthesis of these regulatory responses for their own intracellular survival?

Clear evidence indicates that some AERD patients synthesize excessive numbers of LTs even before any exposure to ASA or NSAIDs [34]. However, AERD patients can have mild, moderate, or severe respiratory disease that is reflected in the baseline synthesis of LTs [34]. Higher concentrations of LTC₄ and thromboxane B₂ were also found in bronchoalveolar lavage fluid taken from AERD patients compared with control asthmatics and normal patients [35]. Sanak and Szczeklik [36] discovered a genetic polymorphism of the LTC₄ synthase promoter region and described an increased prevalence of its variant type in Polish patients with AERD, although the same finding was also noted in bronchial samples from some normal individuals. Not only is there overproduction of LTs in some patients with AERD, but Sousa et al. [37] demonstrated that in AERD—and not in ASA-tolerant asthmatics—nasal inflammatory cells expressed more cysteinyl LT₁ (cysLT₁) receptors. Thus, more receptors were available to receive LTs.

Prostaglandin (PG)D₂, a mast cell-derived prostanoid that is synthesized via the COX-1 and COX-2 pathways, is oversynthesized and secreted in asthmatics with AERD [38]. PGD₂ causes vasodilatation and bronchoconstriction and is a potent chemoattractant for eosinophils, operating through PGD₂ (DP₂) receptors on eosinophils [39]. Therefore, in AERD, not only is there an increase in 5-lipoxygenase (5-LO) products, but at least one prostanoid is also proinflammatory and tends to be oversynthesized in AERD.

PGE₂ plays a special role in the pathogenesis of AERD (Fig. 1). Undersynthesis of PGE₂ or its E receptors (EP₂ or EP₃) diminishes the blocking capabilities of PGE₂ on 5-LO and 5-LO-activating protein (FLAP) or mast cells [40•]. Every study of PGE₂ has concluded that this prostanoid is anti-inflammatory in mast cells. It regulates enzymatic conversion of arachidonic acid to LTA₄ by exerting an inhibitory effect on FLAP and 5-LO. PGE₂ also inhibits discharge of granular mediators from mast cells.

Concerning the pathogenesis of AERD, a pattern is emerging in which many defects in overstimulation of inflammation or underproduction of counter measures, especially in the eicosanoid family, are found in AERD patients. Furthermore, no single genetic defect or promoter gene appears to account for all patients with AERD. Rather, some AERD patients are upregulating LTC₄ synthase, others are upregulating cysLT₁ receptors, and still others are oversynthesizing specific cytokines. At

the opposite end of the equation, some AERD patients are undersynthesizing PGE₂ or EP₂ or EP₃ receptors. Undersynthesis of regulatory cytokines, such as interleukin-10, could also play a role in this concert of events. All these observations fit a theory in which multiple divergences from normal inflammatory pathways could occur in different patients with AERD yet render all patients vulnerable to COX-1 inhibitors. A single gene and its phenotype or a single virus and its genetic stimulation or inhibition of cytokines has not evolved from prior or contemporary research and seems unlikely to do so in the future.

ASA- and NSAID-induced hypersensitivity reactions

In AERD, acute respiratory reactions induced by ASA or NSAIDs contain all the features of immediate IgE-mediated hypersensitivity reactions, but such a mechanism has never been demonstrated. All structurally dissimilar NSAIDs that inhibit COX-1 can cause respiratory reactions in AERD patients upon first exposure to the new NSAID [5••]. Thus, drug hapten-antibody recognition cannot be responsible for these reactions [2].

When AERD patients undergo OACs, increases in urinary LTE₄ are recorded in almost all of them [34]. The same increase in urinary LTE₄ occurs during nasal responses to ASA-lysine [26]. Elevations in LTC₄ and histamine in nasal [41] and bronchial lavage fluid [35] after OACs or bronchial ASA challenges in patients with AERD also have occurred. Therefore, rapid synthesis of new LTs is observed in all patients during ASA-induced respiratory reactions. During ASA-induced respiratory reactions, mast cells release histamine and tryptase and synthesize prostanoids (PGD₂) and LTs, and eosinophils secrete toxic molecules and synthesize LTs (Fig. 1) [5••].

Over the years, it has become clear that increased synthesis of LTs in AERD patients undergoing respiratory reactions to NSAIDs or ASA is secondary to competitive inhibition or disabling of COX-1 enzymes [5••]. COX-1 is a constitutively expressed enzyme that is present in most mammalian cells, including respiratory and gastrointestinal epithelial cells, and in most inflammatory cells. By contrast, COX-2 is only expressed in inflammatory cells and is an inducible enzyme that is highly upregulated by proinflammatory mediators such as cytokines, growth factors, and molecules generated from tissue injury. When COX-1 is inhibited by NSAIDs, a rapid decrease in the synthesis of COX-1 products occurs. The most important undersynthesis of a prostanoid is PGE₂. The “braking” effects of PGE₂ are reduced or disappear, and 5-LO is unopposed, leading to large increases in synthesis of LTs [42]. Reduced PGE₂ synthesis also results in decreased mast cell stability and increased release of histamine and tryptase [40•]. When patients were pretreated with inhaled PGE₂ during OACs, they did not experience respiratory reactions, and urinary LTE₄ did not increase [43]. The failure of COX-2 inhibitors to cross-react in AERD patients is further evidence that inhibiting COX-2 enzymes, which synthesize very little of the total PGE₂ in the patient, does not deplete enough PGE₂ to make a difference. COX-1, which is unaf-

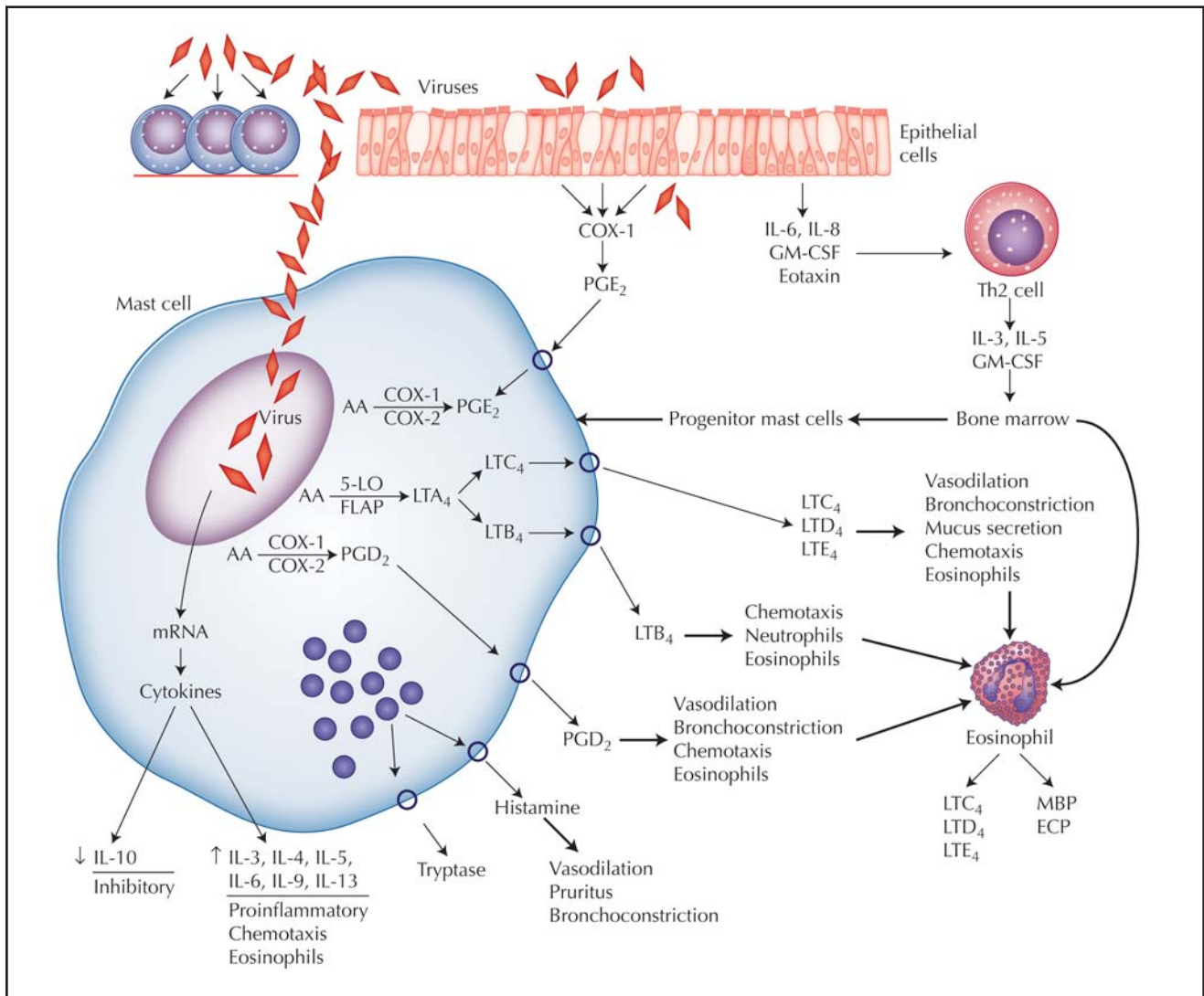


Figure 1. Epithelial cells are infected with viruses, starting an inflammatory cascade through synthesis of cytokines that recruit T-helper type 2 (Th2) cells. Interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate bone marrow cells. Progenitor mast cells and eosinophils leave the bone marrow and migrate to the mucosal viral infection. It is not known whether viruses infect mast cells. However, mast cells become active, and a cascade of mediators leave mast cells and have the listed effects on end organs. Proinflammatory cytokines are synthesized, and IL-10, an inhibitory cytokine, may be undersynthesized. During aspirin reactions, the inhibitory effects of prostaglandin (PG) E_2 are broken, and mediators dramatically increase. Aspirin desensitization occurs when PGD $_2$ and PGE $_2$ are no longer formed because of the inhibition of cyclooxygenase (COX)-1 and COX-2. Aspirin interrupts nuclear factor- κ B transcription. 5-LO—5-lipoxygenase; AA—arachidonic acid; ECP—eosinophil cationic protein; FLAP—5-lipoxygenase activating protein; LT—leukotriene; MBP—major basic protein.

ected by COX-2 inhibitors, continues to provide ample PGE $_2$ to maintain the inhibition of mast cells, and its elimination starts the reaction.

This finding should not be surprising, as the small numbers of inflammatory cells synthesizing PGE $_2$, when compared with the billions of cells expressing constitutive COX-1, account for the discrepancy. That meloxicam does not cross-react with ASA in AERD at low doses (when COX-2 is inhibited) but does cross-react with mild asthma attacks at high doses (when COX-1 is inhibited) provides further evidence that COX-1 inhibition is the key event in the induction of ASA/NSAID-induced respiratory reactions. Finally, the defect of undersynthesizing PGE $_2$ or decreased transcription of EP $_2$ receptors for PGE $_2$ may well

render AERD patients preferentially to underinhibit 5-LO and FLAP when challenged with ASA or NSAIDs.

In addition to increased synthesis of LTs, most patients with AERD have increased expression of cysLT $_1$ receptors on their inflammatory cells [37]. This dramatically tips the equation toward a pronounced increase in end-organ responses to LTs.

LTs are not the only mediators released or synthesized during ASA-induced respiratory reactions. Nasal secretions obtained during ASA-induced reactions contained increased concentrations of histamine, tryptase, LTB $_4$, LTC $_4$, and PGD $_2$ and decreased concentrations of PGE $_2$ [41]. The same was true for bronchial secretions during ASA-lysine-induced lower respiratory tract reactions

[35]. PGD₂ metabolites increased in serum samples during ASA-induced respiratory reactions (Fig. 1) [38].

Treatment

Avoidance of ASA and NSAIDs

The major danger of death from asthma comes from the first full therapeutic dose of ASA/NSAID taken sometime in midlife, particularly if this occurs far from a medical facility. I am not advocating universal avoidance of NSAIDs for all asthmatic patients. Such a recommendation would deny 80% of asthmatics access to these important medications. Whenever practical, giving first-dose NSAIDs in the office to asthmatics with sinusitis, nasal polyps, and anosmia is likely to provide protection through immediate treatment if an asthma attack occurs. In this subset of asthmatics, up to 42% will have a first-dose reaction to any COX-1-inhibiting NSAID [10].

Treatment of the underlying respiratory tract disease

Some AERD patients have such mild disease that it can be controlled with montelukast alone or albuterol as required. Other AERD patients have such severe chronic asthma that they require polypharmacy and still go to emergency departments and hospitals to treat their asthma or die during one of these asthma attacks. Therefore, no universal treatment plan exists for patients with AERD.

Within the population of AERD patients, some require continuous systemic corticosteroids. In a review of 300 AERD patients whose disease was severe enough to be referred for ASA desensitization, systemic corticosteroids were used in short courses in 134 (45%), on a daily basis in 95 (32%), and not at all in 71 (23%) [6]. LT-modifier drugs, such as zileuton (a 5-LO inhibitor) and montelukast (a cysLT₁-receptor antagonist), are commonly used in AERD patients; zileuton has demonstrated efficacy [44], and montelukast also has been shown to positively alter the clinical course in patients with AERD [45]. Simultaneous use of zileuton and a cysLT₁-receptor antagonist has never been formally studied in AERD patients but is used frequently by clinicians, with anecdotal success.

In AERD patients who are also atopic, treatment of underlying allergic inflammation also should be maximized. Allergen avoidance, antihistamines, immunotherapy, and anti-IgE treatment should be strongly considered as primary or adjunctive treatment in AERD patients. It does not make sense to ignore a concomitant disease, such as allergic rhinitis or asthma, and conclude that AERD is the only mechanism driving eosinophilic inflammation in patients with AERD and allergic respiratory disease.

When maximal medical management of nasal polyposis has failed, as is common in AERD patients, referral to an otolaryngologist should be initiated. In fact, many patients begin their medical journey with an otolaryngologist because nasal polyps and anosmia are the most common presenting manifestations of their disease. Nasal

polypectomies, resection of eosinophilic inflammatory tissue, pathologic and bacteriologic/mycotic identification, and widening of sinus ostia are useful interventions in patients with AERD. As a group, AERD patients tend to have a larger burden of polypoid tissue, and postsurgical regrowth of polypoid tissue remains a significant problem [46]. On average, reoperation for nasal polyps is required every 3 years in AERD patients [47].

ASA desensitization

ASA desensitization followed by daily ASA treatment is an effective yet underused treatment. Almost all patients with AERD can be desensitized to ASA. Once desensitized and maintained with ASA (325 or 650 mg twice daily), patients not only enjoy significant improvement in upper and lower respiratory symptoms but now may safely ingest any of the cross-reacting NSAIDs without suffering respiratory reactions [48]. Four long-term studies of patients who underwent ASA desensitization followed by daily ASA ingestion have demonstrated efficacy in reducing upper airway congestion and nasal polyp formation and improving lower airway asthma control [47–49].

ASA desensitization should be considered as a therapeutic option in patients with uncontrolled upper and lower respiratory symptoms, multiple polypectomies, multiple sinus operations, unacceptably high intermittent or chronic systemic corticosteroids, and in those who require ASA for treatment of other diseases [50••].

Conclusions

AERD is a distinct clinical entity characterized by acute ASA-induced respiratory reactions, asthma, nasal polyposis, and chronic hyperplastic eosinophilic sinusitis. If it is not recognized and treated appropriately, AERD has the potential to cause significant morbidity and even mortality, particularly when full doses of ASA or NSAIDs are ingested away from an acute care medical facility. Patients must be educated regarding avoidance of ASA and cross-reacting COX-1 inhibitors to prevent potential life-threatening asthma exacerbations. Treatment of nasal polyp and sinus disease is also important to effectively control asthma and to significantly prevent secondary infections and improve patients' quality of life. ASA desensitization should be considered as add-on treatment for AERD in some patients. We must hope that etoricoxib and parecoxib, new selective COX-2 inhibitors available in Europe, will find their way into the US market over the next few years. Further pharmacologic advances, such as new 5-LO or FLAP inhibitors, antiviral strategies, and genetic identification and manipulations, may provide future benefits to this subgroup of asthmatics.

Disclosure

No potential conflict of interest relevant to this article was reported.

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- Of importance
- Of major importance

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