REVIEW ARTICLE

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Aspirin-Exacerbated Respiratory Disease

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Salicylic acid is found in an extract prepared from the bark of white willow trees and has been used for thousands of years for the relief of fever and pain.[1] In 1897, Felix Hoffmann, a young chemist employed by Friedrich Bayer and Company, acetylated salicylic acid to produce acetylsalicylic acid. By 1899, Bayer had patented the drug, named it "aspirin," and begun selling it around the world. Consumption skyrocketed, with aspirin then used for controlling pain, fever, headache, arthritis, and other diseases.[1] It was not until 1922, in a case report by Widal et al., that respiratory disease exacerbated by aspirin was first described.[2] After an oral challenge with aspirin, a female volunteer with all the hallmarks of underlying respiratory disease had an asthma attack, profuse rhinorrhea, and urticaria. The same reactions occurred after oral challenges with antipyrine, which had been synthesized in 1883 and was the only other available nonsteroidal antiinflammatory drug (NSAID) at that time.

In 1967, Max Samter, an immunologist in the United States who was unaware of the 1922 French report, believed that he had discovered this disease and named it "Samter's Triad" (nasal polyps, asthma, and sensitivity to aspirin).[3] Since then, a number of descriptors of the disease have appeared (e.g., aspirin intolerance, aspirin idiosyncrasy, and aspirin-induced asthma). Aspirin-exacerbated respiratory disease (AERD) became the preferred term in the United States, reflecting a shift away from the implication that the disease occurs only in the lower airways. Although AERD is the preferred term in the United States and other countries around the world, many parts of Europe and the Middle East prefer NSAID-exacerbated respiratory disease.

Clinical Descriptions and Hallmarks of the Disease

AERD is characterized by mucosal swelling of the sinuses and nasal membranes, formation of polyps, and asthma. But unlike most patients with identical clinical features, patients with AERD also have respiratory reactions after ingesting aspirin and other NSAIDs. These reactions typically involve the upper airways (nasal congestion, rhinorrhea, and sneezing) and lower airways (laryngospasm, cough, and wheeze). Less commonly, gastrointestinal symptoms (abdominal pain and nausea) and cutaneous symptoms (flushing and urticaria) occur but are almost always accompanied by some degree of respiratory involvement. AERD is acquired, appearing any time from late childhood to adulthood; the median age at onset is around 30 years.[4,5] On the basis of patients' recollections, about 50% of AERD cases appear after a viral respiratory infection.[6] Ongoing symptoms of AERD are perennial rhinorrhea, nasal congestion, and anosmia, almost always with the addition of asthma. Once the disease has become established, and usually by the time medical evaluation is sought, patients with AERD have nasal polyps and pansinusitis on imaging studies. Most patients with AERD are unable to drink alcoholic beverages without having upper- or lower-airway hypersensitivity reactions; the underlying mechanism is un-

clear.[7] Although some patients report reactivity to any alcoholic beverage, red wine and beer cause reactions in the vast majority of patients, suggesting additional contributions beyond the ethanol component.

AERD does not preclude other provoking mechanisms. These include exacerbations of asthma and rhinitis during viral infections, gastroesophageal reflux, irritant provocations, exercise-induced exacerbations, and IgE-mediated reactions to pollens, dust, animals, and foods.

Patients with AERD are usually referred initially to a head and neck surgeon. In contrast to the outcome after routine sinus surgery in patients without AERD, in most patients with AERD, surgery is followed by rapid and aggressive recurrence of nasal polyps, as early as a few weeks postoperatively.[8]

The severity and progression of AERD vary markedly.[9] At one end of the spectrum, AERD involves only the upper airways[10]; at the other end, AERD causes severe asthma and rhinosinusitis, with remodeling of the upper and lower airways.[11] Among patients with asthma or chronic sinusitis, those with AERD are the most likely to have severe disease that is difficult to manage.[8,11-14]

AERD is never present at birth and rarely clusters in families.[4,5] It is only slightly more common in females than in males[4,5] and is found in all countries except China, where the occurrence is rare.[15] Attempts to find a single AERD gene have failed, and all efforts to find combinations of genetic variations or single-nucleotide polymorphisms have pointed to only partial associations.[16,17] The combination of genetic susceptibility and external respiratory assaults such as virus infections and air pollution continues to be a viable hypothesis for the genesis of AERD.

ATOPIC DISEASES

Among the patients in whom AERD develops in the third decade of life, two thirds have a history of atopy and the other third are free from any allergies.[4] Most investigators accept the view that underlying allergic disease is separate from AERD and not the cause of it. AERD is best classified as a coexisting condition.

REACTIONS TO CYCLOOXYGENASE 1 INHIBITORS

At therapeutic doses, all cyclooxygenase 1 (COX-1) inhibitors, including aspirin, initiate respiratory reactions in patients with AERD (Table 1). As shown in Figure 1, even low doses of aspirin acetylate COX-1, permanently inhibiting function until new enzyme is generated (>48 hours). All other NSAIDs are competitive inhibitors of the COX-1 enzyme channel, with much shorter blockades of COX-1 functions (<12 hours). The larger the doses of COX-1–inhibiting NSAIDs, including aspirin, the larger the ensuing respiratory reactions. The mechanisms by which NSAIDs cause respiratory reactions in patients with AERD were reviewed in detail by Laidlaw and Boyce in 2016.[18] Figures 1 and 2 show the precarious homeostasis of mast cells at baseline and the critical depletion of prostaglandin E_2 (PGE_2) when COX-1 is inhibited. In AERD, PGE_2 scarcely inhibits the inflammatory cascades at baseline, and when PGE_2 is depleted, nothing is available to stop mast-cell discharge and synthesis of additional mediators.[19]

Ibuprofen and indomethacin were introduced into the market in 1962 and 1963, respectively. Both these drugs are potent inhibitors of COX-1. Confirming the observation of Widal et al.,[2] Vanselow and Smith reported in 1967 that oral challenges with aspirin and indomethacin induced respiratory reactions in a patient with AERD.[20] Shortly thereafter, Samter and Beers reported that ibuprofen cross-reacted with aspirin and that the chemical configurations of ibuprofen and aspirin were so different that immune recognition of both drugs was improbable.[3,21]

Table 1 lists NSAIDs that cause respiratory reactions on first exposure in patients with AERD. Most COX-1 inhibitors are sold as tablets or capsules, which take 30 to 90 minutes after ingestion to be absorbed and to circulate and initiate respiratory reactions in patients with AERD. Ketorolac is available in tablet form and in solution for intravenous, intranasal, and intramuscular administration. In patients with AERD, the time from intravenous administration of ketorolac to a reaction is about 15 minutes.[22] At high doses, weak inhibitors of COX-1, such as acetaminophen[23] and salsalate,[24,25] barely induce mild respiratory reactions and only in a minority of patients with AERD (Table 1).

Specific cyclooxygenase 2 (COX-2) inhibitors do not cause respiratory reactions in patients with AERD (Table 1).[26] These larger molecules cannot access the smaller COX-1 channel and can fit only into the wider COX-2 enzymes as competitive inhibitors. Therefore, they cannot interfere with constitutive activity of the COX-1 enzymes in mast

Table 1. Cyclooxygenase 1 (COX-1) and Cyclooxygenase 2 (COX-2) Inhibitors That Trigger Respiratory Reactions in Patients with Aspirin-Exacerbated Respiratory Disease (AERD).*

Medication	Route of Administration
Highly selective COX-1 inhibitors	
Acetylsalicylic acid	Oral (OTC)
Antipyrine–benzocaine	Otic only (OTC)
Benoxaprofen	Oral
Diclofenac	Oral, topical
Etodolac	Oral
Fenoprofen	Oral
Flurbiprofen	Oral
Ibuprofen	Oral (OTC)
Indomethacin	Oral
Ketoprofen	Oral, topical
Ketorolac	Oral, IM, IV, nasal
Meclofenamate	Oral
Dipyrone	Oral
Mefenamic acid	Oral
Naproxen	Oral (OTC)
Oxaprozin	Oral
Piroxicam	Oral
Tolmetin	Oral
Weakly selective COX-1 inhibitors	
Acetaminophen	Oral (OTC)
Choline magnesium trisalicylate	Oral
Diflunisal	Oral
Salsalate	Oral
Highly selective COX-2 inhibitors	
Celecoxib	Oral
Etoricoxib†	Oral
Lumiracoxib†	Oral
Parecoxib†	IV, IM
Preferentially selective COX-2 inhibitors (COX-1 inhibition at high doses)	
Meloxicam	Oral
Nabumetone†	Oral
Nimesulide†	Oral, topical

* In patients with AERD, respiratory reactions are triggered by first exposure to any nonsteroidal antiinflammatory drug (NSAID), except COX-2 inhibitors. Prior drug sensitization is unnecessary for this competitive inhibition reaction of COX-1 and then COX-2 enzymes. Listed drugs are available by prescription only unless designated as available over the counter (OTC). IM denotes intramuscular, and IV intravenous.
† This drug is not available in the United States.

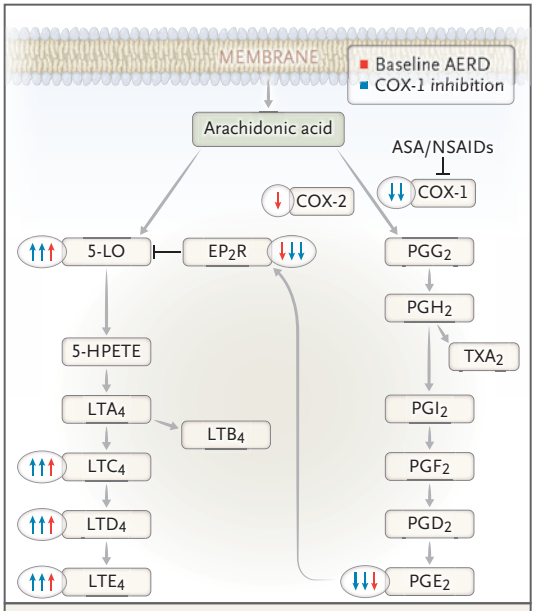

Figure 1. Mechanisms Underlying Respiratory Reactions to Cyclooxygenase 1 (COX-1) Inhibitors.

At baseline, inflammation of the respiratory tract is already ongoing in patients with aspirin-exacerbated respiratory disease (AERD). With COX-1 inhibition by any nonsteroidal antiinflammatory drug (NSAID), the loss of prostaglandin E_2 (PGE_2) inhibitory control leads to massive release of histamine and generation of cysteinyl leukotrienes by mast cells, an event that is unique to AERD. (Prostaglandin D_2 [PGD_2] is pharmacologically inhibited with COX-1 inhibition, but the level greatly increases during reactions through mast-cell and eosinophil activation.) COX-1 inhibition does not block this alternative pathway, which continues unchecked. Red arrows represent abnormal baseline conditions in patients with AERD, and blue arrows indicate changes after COX-1 inhibition. The number of arrows indicates the magnitude of change. ASA denotes acetylsalicylic acid, EP_2R prostaglandin E_2 receptor, 5-HPETE 5-hydroperoxyeicosatetraenoic acid, LT leukotriene (types A_4, C_4, D_4, and E_4), 5-LO 5-lipoxygenase, PG prostaglandin (types G_2, H_2, I_2, and F_2), and TXA_2 thromboxane A_2.

cells, basophils, eosinophils, and platelets, including critical synthesis of PGE_2. Only two COX-2 inhibitors are available in the United States: celecoxib and the 7.5-mg dose of meloxicam. The 15-mg dose of meloxicam causes mild respiratory reactions in patients with AERD, functioning as a partial COX-1 inhibitor (Table 1).[27] Substitution of COX-2 inhibitors for COX-1 inhibitors is a useful strategy in patients with known AERD or

those with unphenotyped asthma in whom AERD has not been ruled out. Unfortunately, COX-2 inhibitors can be obtained only by prescription, which often causes patients with AERD to unknowingly rely on readily available over-the-counter COX-1 inhibitors.

DIAGNOSTIC ROLE OF THE MEDICAL HISTORY

Table 2 lists the types of histories that can be elicited from patients with asthma or nasal polyposis. Obtaining this information is essential because it provides the best clues in determining whether AERD is present. Although 24-hour urinary leukotriene E_4 (LTE_4) measurements may prove useful diagnostically, an observed aspirin challenge, which definitively induces recognizable symptoms and changes in lung function, is currently required to make the diagnosis of AERD.[30] Oral aspirin is commonly used for diagnostic challenges, but experience with nasal and inhaled lysine–aspirin challenges in Europe led to the use of nasal ketorolac as a substitute in the United States.[31-33] More than 80% of patients reporting any history of mild respiratory symptoms after NSAID ingestion will have positive oral aspirin challenges (Table 2).[34] Unfortunately, with the diagnosis based on the patient's history, both underdiagnosis and overdiagnosis of AERD are inevitable. Despite this shortcoming, linking NSAID ingestion to respiratory symptoms is the most important step in identifying patients who should undergo a diagnostic challenge. The second most important step is computed tomographic sinus imaging. A normal sinus study essentially rules out AERD (Table 2).

PREVALENCE

There are no accurate data on the prevalence of AERD in the general population or among patients with asthma, nasal polyposis, or both. A heavy diagnostic burden is placed on the only distinguishing event found exclusively in cases of AERD — namely, a history of a respiratory reaction to aspirin or other COX-1–inhibiting NSAIDs. We performed a meta-analysis to estimate the prevalence of AERD, stratifying potential bias by looking at study types separately and in the aggre-

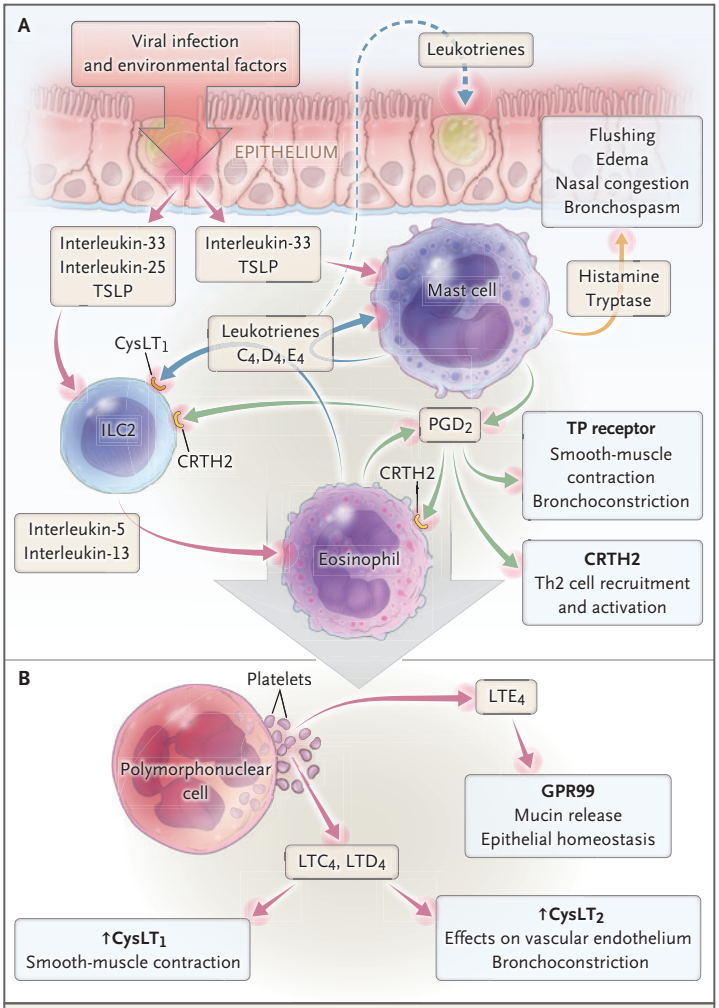

Figure 2. Inflammatory Pathways in AERD.

Type 2 inflammation has a circular path in patients with AERD (Panel A). Allergens, viral infection, and environmental factors are all capable of initiating epithelial injury and release of alarmins, interleukin-33, thymic stromal lymphopoietin (TSLP), and interleukin-25. These upstream cytokines have multiple effects focusing on type 2 inflammatory responses. Type 2 innate lymphoid cells (ILC2) and mast cells in AERD both amplify the responses, leading to eosinophilia and potential feed-forward mechanisms. Leukotrienes enhance these pathways and can control ILC2 responses. Platelet–adherent neutrophils (Panel B) further increase the leukotriene burden in AERD. Despite COX-1 inhibition of prostaglandins, a paradoxical oversynthesis of prostaglandin D_2 (PGD_2) occurs as a result of mast-cell and eosinophil activation through thromboxane (TP) receptors. PGD_2 receptors stimulate the recruitment of type 2 helper T (Th2) cells. Cysteinyl leukotrienes C_4 (LTC_4) and D_4 (LTD_4) act on both cysteinyl leukotriene receptor 1 ($CysLT_1$) and cysteinyl leukotriene receptor 2 ($CysLT_2$). Leukotriene E_4 (LTE_4) has minimal function at $CysLT_1$ and $CysLT_2$ but binds G protein–coupled receptor 99 (GPR99), leading to mucin release and submucosal swelling. CRTH2 denotes chemoattractant receptor-homologous molecule expressed on Th2 cells.

Table 2. Likelihood of AERD on the Basis of Historical Information.*

Historical Information	Likelihood of Positive OAC†
In patients with asthma and opacified sinuses on imaging	
Respiratory symptoms within 90 min after ingestion of an NSAID on one occasion	80%
Respiratory symptoms within 90 min after ingestion of 1 or 2 NSAIDs on ≥2 occasions	89%
Mild respiratory symptoms (treated by patient with antihistamines or nebulizer)	80%
Moderate respiratory symptoms (treated in medical office or emergency department)	84%
Severe respiratory symptoms (requiring hospitalization)	100%
Asthma and sinus disease in the absence of exposure to NSAIDs	42%
Daily aspirin therapy (81 mg) for cardiovascular prophylaxis; desensitization with first exposure‡	Unlikely
Additional baseline disease characteristics	
Asthma but normal sinus on CT scans§	Extremely unlikely
Nasal polyps and pansinusitis on imaging, without asthma (upper-airway AERD)	Unlikely
Asthma attacks after ingestion of any alcoholic beverages	Highly likely
Complete anosmia associated with nasal polyps	Highly likely
Rapid regrowth of nasal polyps after first sinus or polyp resection	Highly likely
Nasal polyps and asthma in childhood	Extremely unlikely

* Data are from Cardet et al.,[7] Kim and Kountakis,[8] Mascia et al.,[12] Dursun et al.,[28] and Lee-Sarwar et al.[29] Respiratory symptoms comprise the following, alone or in any combination: rhinorrhea, nasal congestion, sneezing, chest tightness, wheezing, shortness of breath, and need for an albuterol nebulizer. Tolerance of COX-2 inhibitors is expected in AERD, and COX-2 inhibitor use should not influence the diagnostic assessment.

† A positive oral aspirin challenge (OAC) is the definitive diagnostic test for AERD.

‡ Daily aspirin therapy does not preclude a diagnosis of AERD. Patients may accidentally desensitize themselves or start taking aspirin before the development of AERD. Stopping aspirin therapy or extending the interval between doses to more than 72 hours unmasks the hypersensitivity, and positive challenges may be seen. Exposure to acetaminophen at a dose of 1000 mg or higher results in modest COX-1 inhibition and triggers mild reactions in 33% of patients with AERD.

§ AERD is an acquired disease and ultimately involves mucosal swelling of the entire respiratory tract. A reaction to an NSAID can occur early in the development of the disease, before sinus opacification is identified on computed tomographic (CT) scans but after the onset of asthma. AERD is usually diagnosed at a later stage of the disease.

gate.[34] Oral aspirin challenges are the accepted standard for diagnosing AERD but are not performed in most prevalence studies. In fact, reaction information reported by patients is used in most studies. In our meta-analysis, the prevalence of AERD was 7.2% in the general population of patients with asthma, 14.9% among patients with severe asthma, 9.7% among patients with nasal polyps, and 8.7% among those with chronic sinusitis.[34] Furthermore, oral aspirin challenges were positive in 20 to 42% of patients with nasal polyps, asthma, and chronic rhinosinusitis but no known exposure to COX-1–inhibiting NSAIDs.[28,35,36] AERD is not rare. On the basis of a disease prevalence of 7.2% and 19 million patients in the United States who have asthma, a total of 1,368,000 patients have AERD.

Using a computerized search strategy for a large electronic health system database, Cahill and colleagues found that 12.4% of patients who fulfilled the critical components of the AERD diagnosis (nasal polyps, asthma, and respiratory reactions to NSAIDs) did not have that diagnosis in their medical records and had not been referred for oral aspirin challenges or desensitization.[37]

NON-AERD HYPERSENSITIVITY TO NSAIDS

Hypersensitivity reactions to individual NSAIDs through immune recognition may trigger anaphylaxis. Hives after ingestion of a specific NSAID or flares of chronic urticaria after exposure to any COX-1 inhibitor have nothing to do with AERD.

PATHOLOGICAL AND PHARMACOPATHOLOGICAL FEATURES OF AERD

In 1971, Vane published his explanation for why aspirin and other COX-1 inhibitors cross-react in patients with AERD.[38] Inhibition of COX-1 deprives inflammatory cells of the internal synthesis of prostaglandins (Fig. 1), particularly the protective PGE_2. In 1975, Szczeklik and colleagues definitively showed that inhibition of prostaglandins through increased doses of NSAIDs correlated perfectly with the same drug's ability to induce asthma reactions in patients with known AERD.[39]

These findings provided a mechanism to explain hypersensitivity reactions in patients with AERD; however, much more about AERD remains confounding. Although AERD is characterized by high eosinophil levels with increased numbers and activity of mast cells, no evidence suggests that the disease is the consequence of antigen-specific IgE mechanisms. Several lines of evidence now point toward the role of innate mucosal immune responsiveness in directing a potent type 2 immune response (Fig. 2). Still unanswered are questions about whether the inciting event is virus-induced or toxin-induced injury and why the inflammatory responses fail to resolve spontaneously.

Specifically, the innate cytokines thymic stromal lymphopoietin (TSLP), interleukin-25, and interleukin-33, released from epithelia, are critical in the early steps of this innate type 2 inflammatory response.[40] Buchheit et al.[41] showed that TSLP is directly involved in the synthesis of PGD_2 in mast cells. Liu et al.[42] subsequently identified interleukin-33 as a central hub directing mast-cell activation and eosinophil recruitment after epithelial injury (Fig. 2).

Although innate, epithelia-derived signals might be critical upstream mediators in AERD, a central component of the disease is up-regulated cysteinyl leukotriene. Central observations in AERD are the enhanced response to cysteinyl leukotrienes[43,44] and elevated cysteinyl LTE_4 levels both at baseline and during acute reactions.[45] LTE_4 is capable of driving pulmonary eosinophilia.[46,47] As the stable end-product of leukotriene metabolism, LTE_4 plays a critical and probably underappreciated role. Lee et al. initially described LTE_4-induced enhancement of airway responsiveness to histamine, an effect not seen with leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4), suggesting the presence of a unique LTE_4 receptor.[48] After aspirin desensitization, LTE_4-induced bronchospasm is markedly diminished in patients with AERD, a response that does not occur in patients with aspirin-treated asthma who do not have AERD.[43] G protein–coupled receptor 99 (GPR99), a specific LTE_4 receptor, might transduce the biologic effects previously described.[49,50]

Patients with AERD have diminished effects of PGE_2, a key stabilizer of cyclooxygenase that also has an antiproliferative effect. Mediated through altered expression of the EP_2 receptor, this effect was shown to be under epigenetic control, potentially influenced by infectious or inhaled environmental toxins.[51] Impairment in appropriate COX-2 up-regulation might further diminish the production of PGE_2, exacerbating the imbalance.[52] The observations that eosinophils in AERD may have unique interferon gamma production and responsiveness,[53] that platelets adherent to leukocytes can markedly augment cysteinyl leukotriene production in AERD,[54] and that a subgroup of difficult-to-desensitize patients with AERD have poor suppression of PGD_2 after aspirin administration[55] all point to AERD as a unique inflammatory airway disease.

MEDICAL TREATMENT

AERD is treated medically in a stepwise fashion according to established guidelines for the management of asthma and chronic sinusitis. Management usually progresses through the use of controller inhaler medications and leukotriene-modifier drugs, with the possible use of biologic agents as indicated for asthma. The upper airways are similarly treated with topical glucocorticoids, and if this treatment fails, it is necessary to add antihistamines, leukotriene modifiers, and systemic glucocorticoids. Zileuton, an inhibitor of 5-lipoxygenase, merits attention, since it partially blocks the formation of all cysteinyl leukotrienes, including LTE_4, and has proved to be effective in the treatment of AERD.[56] LTE_4 would not be markedly affected by the $CysLT_1$ receptor antagonists montelukast, zafirlukast, and pranlukast. Most patients with AERD have difficulty

managing airway inflammation and are therefore candidates for aspirin desensitization and daily aspirin therapy. In fact, the only unique treatment for AERD that is currently available is aspirin desensitization.

SURGICAL TREATMENT

By the time they consult a physician, many patients with AERD have severe nasal polyposis. At this stage, the only available medical intervention is systemic glucocorticoid therapy, which eventually fails or has unacceptable side effects. Surgical debulking of nasal polyps and functional endoscopic sinus surgery provide ventilation of the sinuses and facilitate the delivery of topical medications as well as removal of an inflammatory nidus (eosinophilic polyps).[57-59] Since polyps recur rapidly, it is recommended that aspirin desensitization be performed shortly after sinus surgery.[60,61] Although preventing further surgical intervention is a cardinal goal of medical therapy, repeat polypectomies are common despite medical management.

ASPIRIN DESENSITIZATION AND TREATMENT WITH ASPIRIN

Drug desensitization, also called induction of drug tolerance, can be used for selected medications. Aspirin desensitization is achieved by starting at low oral doses of aspirin (approximately 40.5 mg) and gradually increasing the dose over a period of 1 to 3 days, during which drug-induced reactions become milder and shorter and then disappear. When the target dose of 325 mg is achieved, any additional doses of aspirin or other COX-1–inhibiting NSAIDs do not induce hypersensitivity reactions.

Desensitization to aspirin was first performed by Widal and associates in 1922.[2] In 1976, Zeiss and Lockey reported a 72-hour refractory period after a positive oral challenge with indomethacin.[62] Also in 1976, Bianco and colleagues[63] induced asthma with inhaled aspirin–lysine in a patient with AERD. For the next 72 hours, inhalation of the same provoking doses of aspirin–lysine did not induce any asthmatic response (refractory period).

In 1980, during a study of mediator release after aspirin-induced asthma in a patient with AERD, we used aspirin at a dose of 325 mg to induce a large respiratory reaction.[64] The next day, a 325-mg dose of aspirin was again administered, and no respiratory reaction occurred. The patient reported to us that she could breathe through her nose and smell for the first time in years. This result led to our first treatment trial with daily aspirin in the desensitized state, which decreased nasal mucosal swelling but did not change the presence of asthma; a methacholine inhalation challenge still induced bronchospasm.[64] During the next year, systemic glucocorticoids were discontinued in the first patient and reduced by 50% in another patient, with continued patency of the nasal passages in both patients. This study was followed by confirmatory studies in other centers[65-70] and at the Scripps Clinic,[71-73] all of which showed significant improvement in rhinosinusitis outcomes. Improvement in asthma outcomes was seen in some patients but was not consistently observed in all the studies. Table 3 summarizes the therapeutic benefits of aspirin desensitization in patients with AERD.

The mechanisms behind effectiveness in the treatment of AERD have been only partly untangled. It is not simply achieving a state of tolerance to aspirin that has a therapeutic benefit, since the dose necessary to improve airway inflammation is generally much higher than that needed to start a respiratory reaction or maintain desensitization. Of the many observations noted, down-regulation of the LTC_4 receptors,[74] decreases in inflammatory PGD_2,[55] decreased effects of LTE_4,[75] and effects on interleukin-4 expression through STAT6 down-regulation[76,77] provide opportunities to understand the mechanism underlying this benefit (Table 3).

Aspirin desensitization, followed by aspirin treatment at a dose of 325 to 650 mg twice daily, is now the standard of care for patients with AERD after debulking of nasal polyps and sinuses has been performed (within 3 to 4 weeks after the first sinus polyp operation).[78] Aspirin desensitization is performed in the clinic under medical supervision, followed by institution of daily aspirin treatment in the desensitized state. Aspirin can be discontinued for 48 hours without loss of desensitization. While taking daily aspirin, patients are also protected from inadvertent exposure to COX-1 NSAIDs, since cross-desensitization to all NSAIDs is universal. Outpatient aspirin

Table 3. Consequences of Aspirin Desensitization, Followed by Daily Aspirin Treatment, in Patients with AERD.

Before Aspirin Desensitization	Aspirin Desensitization and Daily Aspirin Therapy
Nasal congestion	Nasal decongestion, with improved patency
Anosmia	Improvement in sense of smell
Mean no. of viral rhinosinusitis episodes, 6 per yr	Mean no. of viral rhinosinusitis episodes, 1–2 per yr
Aggressive formation of nasal polyps	Reduction in nasal polyp formation
Disturbed sleep due to nasal obstruction	Restorative sleep on clinical observation
Mean interval between sinus or polyp surgeries, 3 yr	Mean interval between sinus or polyp surgeries, 9 yr
Uncontrolled asthma	Improved asthma control
Need for systemic glucocorticoids	Decreased need for systemic glucocorticoids
Marked impairment in quality of life	Quality-of-life scores significantly improved
High costs of medical and surgical care	Low costs of desensitization and daily aspirin
Ongoing reactivity to COX-1–inhibiting NSAIDs	Protection from NSAID reactions

desensitization, followed by daily aspirin therapy, reduces health care expenditures for the management of AERD, since the costs of this approach are much lower than the costs of additional sinus surgery and outpatient and emergency department visits.[79] In a large study involving patients with AERD, revision sinus surgery was needed every 3 years, on average, before aspirin desensitization; after desensitization and daily treatment with aspirin, the mean interval for sinus revision surgery was 9 years.[80] Some patients had no recurrence of nasal polyposis.

Not surprisingly, there are two complications of long-term aspirin desensitization treatment. The first is gastric pain or ulcer caused by diminished synthesis of gastric prostaglandin (PGI_2) formation and inadequate repopulation of gastric mucosal cells (occurring in <15% of patients).[72,73,81] The second complication is bleeding, usually in the skin (ecchymosis) but occasionally in the nose, bronchi, bladder, or gastrointestinal tract.

Physicians caring for patients with AERD should not attempt aspirin desensitization without special training and appropriate nursing supervision.[82] The procedure is not for the novice and should be conducted in a dedicated diagnostic and treatment center where severe reactions can largely be prevented and those that occur can be promptly identified and treated. Aspirin desensitization centers are scattered throughout the United States and the world, particularly in large group practices, academic centers, and large allergy groups, where aspirin desensitization procedures are routinely performed in the presence of leukotriene-modifier blockade to mitigate lower respiratory tract symptoms.[83] Aspirin desensitization protocols focus on safety, speed of completion, and comfort. Differences in protocols are debated,[78,84-86] but all procedures accomplish the same end result — namely, administration of a full 325-mg aspirin tablet without any respiratory signs. One of two results occurs during aspirin challenges. If the challenge is negative, the patient continues to use NSAIDs as needed. If the challenge is positive, incremental increases in the aspirin dose are continued until desensitization is achieved. Thus, during diagnostic aspirin challenges, an accurate diagnosis of AERD is established, and aspirin desensitization treatment is initiated.

Awareness of AERD continues to be overshadowed by the false assumption that it is a rare, esoteric disease. This misperception is combined with unfounded safety concerns about diagnostic oral aspirin challenges. Clinicians should realize that aspirin desensitization, followed by daily aspirin therapy, is a disease-specific treatment that offers a benefit for the majority of patients with AERD. Now that phenotyping in asthma and sinus disease can guide treatment decisions, AERD is a diagnosis worth considering.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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