Aspirin-exacerbated respiratory disease: Prevalence, diagnosis, treatment, and considerations for the future

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ABSTRACT

Aspirin-exacerbated respiratory disease (AERD) is a late onset condition characterized by the Samter triad (aspirin sensitivity [as well as sensitivity to any nonselective cyclooxygenase inhibitor], nasal polyps, asthma) and additional features, including eosinophilic chronic rhinosinusitis, hypereosinophilia, anosmia, frequent absence of atopy, and, intolerance to ingestion of red wine and other alcoholic beverages. The diagnosis is rare, and, because of this, it is also often missed by physicians. However, it is highly overexpressed in patients with severe asthma (and severe chronic rhinosinusitis with nasal polyps), which makes its recognition essential. For this review, we considered mechanisms involved in the pathogenesis of this disease and discussed the clinical symptoms of AERD. We also discussed the role of aspirin desensitization in the treatment of AERD. Also, we considered medications (e.g, leukotriene modifiers) and surgical interventions that have a role in the treatment of AERD.

Aspirin-exacerbated respiratory disease (AERD) was originally defined in 1922 as discussed by Stevenson and Szczeklik[1] and Widal et al.[2] However, clues regarding its existence were evident even earlier than this. A decade before, Gilbert[3] first noted an aspirin-induced asthma attack, and, in 1902, Hirschberg[4] described adverse reactions to aspirin in Germany, only 4 years after aspirin was introduced into the market. Despite the evidence, AERD was not widely recognized until 1968 when Samter and Beers[5,6] described patients with nasal polyps (NP), asthma, and aspirin sensitivity, a triad of symptoms ultimately known as the Samter triad.[1,5,6]

It has become clear that clinicians routinely miss the diagnosis of AERD because of an insufficient index of suspicion. For example, when considering all the patients with a diagnosis of asthma, those with AERD comprise only 0.6–2.5% of this population.[7] However, AERD represents 14.9% of all the patients with severe asthma and 8.7% of the patients with chronic rhinosinusitis with nasal polyps (CRSwNP).[7] Furthermore, aspirin intolerance occurs in as many as 20% of patients with adult onset asthma without sinus disease.[8,9] For this review, we considered the mechanisms involved in this disease and discussed the clinical symptoms of AERD. We also discussed the role of aspirin desensitization in the treatment of AERD. We considered medications that have a role in its treatment.

NATURAL HISTORY AND PREVALENCE OF DISEASE

Unlike other allergic inflammatory conditions, AERD develops in the third or fourth decade of life.[1] The disease has a male predominance (2.3:1)[10]; when diagnosed in women, the disease is usually more severe.[11] In most studies, rhinitis symptoms typically preceded asthma by 1–5 years, and these symptoms can be severe, including chronic congestion, anosmia, and NP.[1,9]

PATHOPHYSIOLOGY AND MECHANISMS OF DISEASE

The underlying respiratory and sinus inflammatory processes of AERD activate an intense infiltration of mast cells, basophils, and eosinophils into the mucosa that synthesize and secrete high levels of cysteinyl leukotrienes (CysLT).[12,13] Mast cells also release histamine, tryptase, and prostaglandin (PG) D_2, vasodilating and bronchoconstricting agents that augment the leukotriene (LT) response. Patients with AERD displayed dramatic upregulation of two essential enzymes involved in CysLT synthesis: 5-lipoxygenase (5-LO) and LTC_4 synthase.[14–16] This overexpression drives both the constitutive overproduction of CysLTs and the life-threatening surge that occurs with ingestion of aspirin and other nonselective cyclooxygenase (COX) inhibitors.[17]

In addition to their overproduction, these patients display greatly enhanced sensitivity to the CysLTs, which reflects overexpression of the CysLT receptors.[18,19] As indicated by the distinct sensitivity of these patients to LTE_4, AERD is likely also associated with enhanced expression of one or more of the newly described selective LTE_4 receptors.[20–22] Both blood and sinonasal tissue of patients with AERD have a significant number of platelets adhered to neutrophils, monocytes, and eosinophils.[23] Platelets express LTC_4 synthase and can use it to generate CysLTs via transcellular transfer of LTA_4 derived from these 5-LO–expressing leukocytes. It is estimated that up to 70% of CysLTs produced in AERD are generated via this mechanism.[23,24]

CHRONIC SINUSITIS WITH NPs

Patients with AERD have evolving sinusitis that starts as mild mucosal inflammation and progresses into a severe persistent disease that often completely fills the sinus cavities with inflammatory tissue and becomes associated with NP.[1] The NPs are intensely eosinophilic, and most patients with AERD have anosmia.[1,25] Computed tomographies of subjects with AERD showed pansinusitis and are typically some of the worst seen in chronic sinus disease, with complete or near-complete opacification of the sinuses.[26] In reflecting the progressive nature of this inflammatory process, surgery is unlikely to be curative. Even when followed by optimal medical therapy, patients with AERD typically required multiple revision surgeries in their lifetime.[1,10]

ASPIRIN SENSITIVITY

In patients with AERD, aspirin and other nonselective nonsteroidal anti-inflammatory drugs (NSAID) that inhibit COX-1 induce unique

Table 1 Aspirin challenge

Before challenge, the patient must stop β-blockers and ACE inhibitors

Placebo challenge can be conducted a week before challenge or if the patient's baseline FEV_1 is the same as a previous best value and the patient has not required his or her albuterol in the past week, then placebo challenge can be skipped

FEV_1 should be measured every hour and as warranted

FEV_1 should be at least 1.5 L and ≥60% of predicted value

Challenge schedule:

Time	Day 1 Dose, mg	Day 2 Dose, mg
8:00 A.M.	20–40	100–160
11:00 A.M.	40–60	160–325
2:00 P.M.	60–100	325*

If the patient did not react to 325 mg of aspirin, then he or she will not react to 650 mg; therefore, if no reaction occurs with the 325-mg dose, it is a negative challenge result

ACE = Angiotensin-converting-enzyme; FEV_1 = forced expiratory volume in 1 second.

Table 2 Ketorolac challenge

To prepare ketorolac: mix ketorolac 60 mg/2 mL with 2.75 mL saline solution into an empty spray bottle from the pharmacy; prime 5 sprays, then each spray actuates 1.26 mg of solution

Instruct the patient to tilt his or her head down while spraying and sniff gently to avoid swallowing solution

Contraindications: complete nasal obstruction

Challenge schedule:

Time	Dose
Day 1	
8:00 A.M.	1 spray (1.26 mg)
8:30 A.M.	2 sprays (1 each nostril)
9:00 A.M.	4 sprays (2 each nostril)
9:30 A.M.	6 sprays (3 each nostril)
10:30 A.M.	60 mg of aspirin
12:00 P.M.	60 mg of aspirin
3:00 P.M.	Discharge instructions
Day 2	
8:00 A.M.	150 mg of aspirin
11:00 A.M.	325 mg of aspirin
2:00 P.M.	Discharge instructions

If there is no reaction 3 hours after the 325-mg dose, then this is a negative challenge result

non–immunoglobulin E (IgE) mediated reactions that consist of attacks of rhinitis and asthma.[1] COX-2 inhibitors, including celecoxib, are generally (but not always) tolerated, but there is a somewhat greater risk of reaction with less selective COX-2 inhibitors, *e.g.,* meloxicam, especially at higher doses.[5,6,27] Despite general tolerance of selective COX-2 inhibitors in patients with AERD, it is recommended that test doses be performed under strict and careful clinical purview if these drugs are required. Reactions to acetaminophen are unusual but can occur.[28–32] The dogma indicates that reactions in patients with AERD are triggered by the inhibition of COX-1, which is not a biologic activity of nonaspirin salicylates and, as such, dietary salicylates are generally not thought to trigger reactions. However, results of recent research showed that a low-salicylate diet perhaps leads to a reduction in symptoms in some patients with AERD.[33] Although limited by being a single-blind study, this finding indicated that, in patients who are refractory to regular management, one might consider a low salicylate diet in addition to typical treatments. Reactions to aspirin in patients with AERD do not develop until systemic concentrations of these agents achieve pharmacologically active concentrations and, as such, generally occur 30–90 minutes after a therapeutic oral dose but can be delayed up to 3 hours after ingestion. Symptoms include a spectrum of respiratory reactions, including rhinitis, flushing, congestion, laryngospasm, and asthma exacerbations.[1]

ASTHMA

Asthma is not always present, thus, the current preference for the term AERD rather than "aspirin intolerant asthma." Typically, in AERD, asthma symptoms develop ~1 to 3 years after the development of rhinitis but can occur even later or, in certain instances, never develop.[11] When present, the asthma of AERD, much like the sinus disease component, is severe and difficult to treat. AERD is also linked to increased airway remodeling, which results in increased residual volume and diminished diffusing capacity.[26,34]

GASTROINTESTINAL AND DERMATOLOGIC REACTORS

Recently, Cahill *et al.*[35] described a new phenotype of AERD. These patients have predominant gastrointestinal and dermatologic findings after exposure to aspirin and are frequently unable to tolerate aspirin desensitization, despite the use of a CysLT receptor antagonists. Symptoms with exposure to COX-1 inhibitors include stabbing abdominal pain, nausea, watery diarrhea, and an erythematous and pruritic macular rash that erupts on the distal extremities and palmar surfaces and not accompanied by urticaria or angioedema. These patients have higher baseline levels of CysLTs and demonstrate no suppression of prostanoid synthesis at threshold aspirin doses.[35] Specifically, they were found to produce significantly more PGD_2, a potent bronchoconstrictor, during the reactions in comparison with the larger AERD population that tolerated aspirin desensitization.[35,36]

DIAGNOSIS

Diagnosis of AERD can be determined with some degree of certainty in a patient with more than one compelling history of a reaction to aspirin or other nonselective NSAID, especially in the setting of extensive chronic rhinosinusitis, NPs, anosmia, and severe asthma. Interestingly, up to 70% of these patients report sensitivity to red wine and other alcoholic beverages, and this history may also indicate the diagnosis of AERD.[37] There is no reliable *in vitro* diagnostic test for AERD, and, as such, in the absence of a history of aspirin or NSAID use or an ambiguous history of symptoms after exposure, the patient should be referred for aspirin challenge to receive a definitive diagnosis.[1,10,38,39] Diagnostic challenges must be performed without LT modifiers (in contrast to desensitization [as described below]) because these agents can completely mask the symptoms and signs of a reaction.[17,40–42] As such, this diagnostic tool must be used with caution because the expected reaction to aspirin in a patient who is allergic has the potential to induce severe bronchospasm.[10]

Aspirin challenge should only be performed after confirmation that the patient's forced expiratory volume in 1 second is within 10% of his or her previous best values and also is ≥60% of the predicted value, and it is imperative that the patient's asthma symptoms are well controlled at the time of challenge. Responses to aspirin can be delayed by as much as 90 minutes or more after ingestion; therefore, progressive doses should be at least this far apart, and the physician must be prepared to monitor the patient for 2–3 hours after ingestion. Oral aspirin challenge can be performed by using graduated doses of aspirin given over 2 days (Table 1).[43] The dose immediately below the reacting dose for provocation challenge can be used as the starting dose for a subsequent desensitization if required.
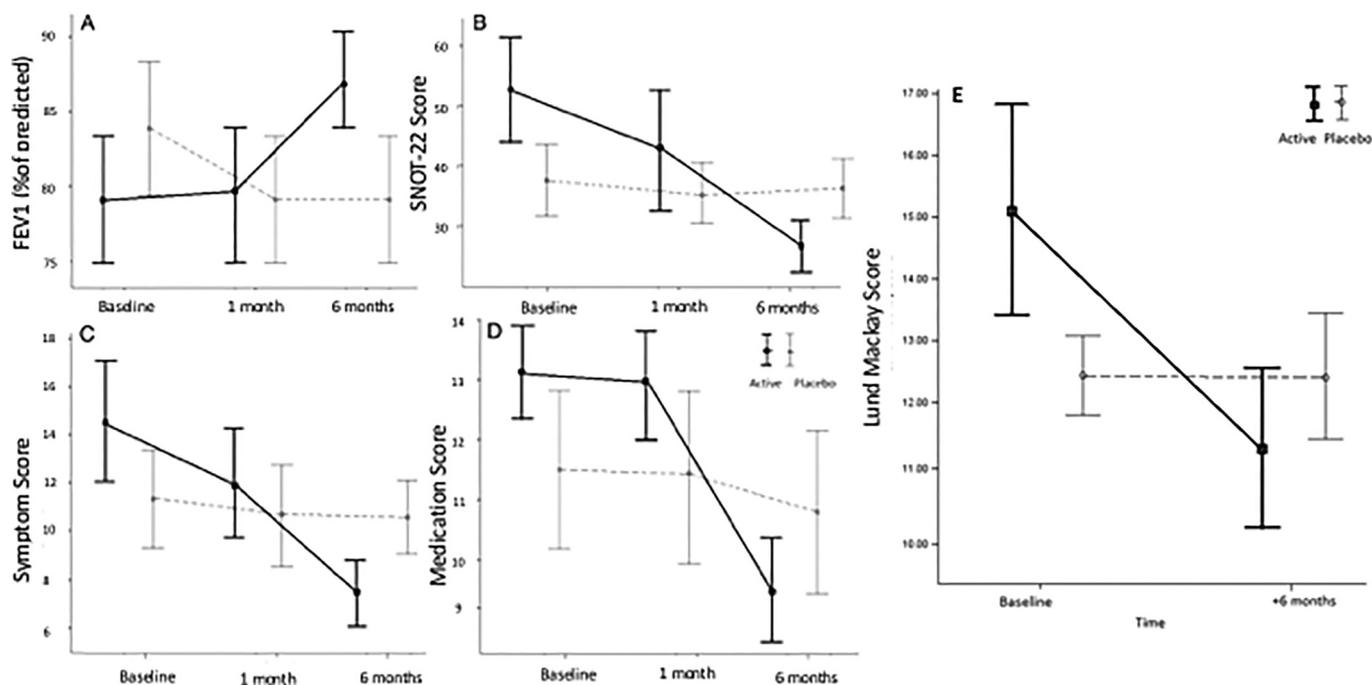
Figure 1. *Double-blind placebo-controlled trial of aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD). Analysis of the data supported significant improvements in forced expiratory volume in 1 second (FEV$_1$) (A), 22-item Sino-Nasal Outcome Test (SNOT-22) scores (B), symptom scores (C), and medication scores (D). (E) Further, there is evidence of improved computed tomography scores at 6 months (Lund-Mackay) (from Ref. 57) (republished with permission).*

An alternative and perhaps safer approach to evaluate aspirin sensitivity is to perform diagnostic nasal ketorolac challenge. This method is not indicated for patients with severe nasal obstruction, including those with significant polyposis. To perform this procedure, liquid ketorolac is diluted into a spray container that will deliver ketorolac intranasally. Doses are administered at 30-minute intervals in a progressive fashion, as shown in Table 2. If the patient does not experience any nasal symptoms or bronchospasm with ketorolac, then oral challenges of aspirin are given at 2–3 hour intervals (Table 2).

BIOMARKERS FOR DIAGNOSIS OF AERD

Because of the inherent risks associated with diagnostic aspirin challenge in patients who may have AERD, researchers are evaluating other ways to confirm aspirin sensitivity. Several biomarkers have been evaluated, and the most promising is 24-hour urinary LTE$_4$. Higher baseline levels of urinary LTE$_4$ levels are typical in AERD and, in contrast to patients with aspirin-tolerant asthma, these levels dramatically increase after aspirin challenge.[44,45] Follow-up studies demonstrated that $\geq$166 pg LTE$_4$/mg creatinine indicates the presence of AERD with 89% specificity, whereas a $\geq$241 pg LTE$_4$/mg creatinine discriminated subjects with "challenge-confirmed" aspirin sensitivity with 92% specificity.[46]

Exhaled nitric oxide (FeNO) levels is used as a biomarker for assessing acute bronchospasm and for supervising asthma control over time.[44,47,48] A recent study discovered that giving low-dose aspirin (40 mg) and measuring FeNO levels 1 hour later produced a significant decrease from baseline in mean FeNO by 19% in patients with AERD. In the study, FeNO had a sensitivity and specificity of 90% and 100%, respectively, for identifying AERD. In contrast, patients with aspirin tolerant asthma had increased or stable FeNO levels.[44] Due to the possibility of severe reactions during standard aspirin challenge, this diagnostic tool needs to be further investigated because of the potential for a more-convenient diagnosis.

TREATMENT

Symptomatic control of both the upper and lower airway is essential in preventing asthma exacerbations and airway remodeling, and in improving overall quality of life. Treatment of AERD begins with avoidance of aspirin and NSAIDs.[1] To diminish nasal inflammation and cease polyp formation, intranasal steroids can be beneficial.[1,49] This may prove more effective after a 2- to 3-week course of systemic corticosteroids, which will aid in shrinking NPs and will at least temporarily reestablish sinus drainage and accessibility of nasally administered agents into the sinuses. As with any patient with asthma, lower airway symptoms require treatment with high-dose inhaled corticosteroids, with or without add-on long-term controllers. Unfortunately, a subset of patients with AERD will gradually require continuous systemic corticosteroids. In one study, 95 of 300 patients (32%) with AERD were found to use systemic corticosteroids on a daily basis, whereas 134 (45%) were found to need short courses.[1,10] As systemic steroids become regularly used in patients with AERD, the risk for significant adverse effects increases.

LT MODIFIERS

As discussed in Pathophysiology and Mechanisms of Disease, AERD is uniquely defined by the excessive production of CysLTs. These mediators drive the severity of the disease, as demonstrated by the ability of LT modifiers, such as zafirlukast or montelukast, to improve lung function, decrease rescue bronchodilator use, reduce symptoms, and improve quality of life.[1,50] Furthermore, CysLTs are particularly important in driving the bronchospastic response to aspirin and other COX inhibitors, and the concomitant use of these agents greatly attenuates these reactions.[51–53] Inhibition of 5-LO through the use of zileuton also improves symptoms in AERD.[1] In fact, this medication seems to be uniquely capable of improving upper respiratory symptoms in the disease.[54] A study by Dahlen *et al.*[50,55] showed significant improvement in smell, rhinorrhea, and congestion with the administration of zileuton. Although these med-

Table 3 Aspirin desensitization

The patient must stop β-blockers, ACE inhibitors, and antihistamines before desensitization

Premedications: (Start 24 hr before desensitization): prednisone 20 mg b.i.d., montelukast 10 mg b.i.d., Zileuton CR 1200 mg b.i.d.

Medications at bedside for systemic reaction: methylprednisolone 125 mg IV, albuterol 0.083% (3 mL) for nebulizer, famotidine 20 mg IV, epinephrine 1:1000 0.3 mL, diphenhydramine 50 mg IV, ipratropium 500 μg for nebulizer

Representative protocol:

Time	Day 1 Dose	Day 2 Dose
8:00 A.M.	1/4 Baby aspirin (20 mg)	1 Baby aspirin (81 mg)
10:00 A.M.	1/2 Baby aspirin (40 mg)	2 Baby aspirin (160 mg)
12:00 P.M.	1/2 and 1/4 Baby aspirin (60 mg)	1 Aspirin (325 mg)
2:00 P.M.	1 Baby aspirin (81 mg)*	2 Aspirin (650 mg)*

Monitoring:

1. Vital signs every hour during desensitization, then as needed
2. Obtain baseline FEV_1 by spirometry; precalculate a 20% reduction in FEV_1 by multiplying FEV_1 in liters by 0.8
3. Obtain spirometry (FEV_1) before each aspirin dose, every hour, and as needed; if severe shortness of breath or if FEV_1 decreases by >20%, give nebulized albuterol and notify physician
4. If systolic BP is <90 mm Hg, give epinephrine 1:1000 0.3 mL intramuscular and notify physician
5. Rhinorrhea, nasal congestion, flushing: check FEV_1 and BP; if rhinorrhea is accompanied by a decrease in FEV_1 by 20% or if systolic BP is <90 mm Hg, treat as above and notify physician: for rhinorrhea, nasal congestion or flushing alone, give diphenhydramine 50 mg IV and notify physician

Discharge medications:

Two aspirins 325 mg by mouth, b.i.d.

Consider Nexium or other proton pump inhibitor or H_2 blocker for gastric lining protection

ACE = Angiotensin-converting-enzyme; b.i.d. = twice a day; IV = intravenous; FEV_1 = forced expiratory volume in 1 second; BP = blood pressure.
*Observe patient for 3 hr after final dose.

ications improve symptoms in an additive manner, they seldom "stand alone" in the treatment of AERD.

ASPIRIN DESENSITIZATION

After confirming that the patient, indeed, is aspirin allergic, one should proceed with aspirin desensitization, given the usual inadequate control of AERD achieved with standard medical and surgical therapies. Aspirin desensitization in these patients improves asthma and sinus symptoms as well as slows NP regrowth after surgery, which thus increases the time to surgical revision.[56–59] Most importantly, aspirin desensitization can decrease oral steroid use.[60] Twice daily aspirin, 650 mg, not only improved nasal symptoms but also improved lung function, decreased the need for medications, improved quality of life, and improved sinus computed tomography scores in a randomized, double-blind, placebo-controlled study done by Esmaeilzadeh et al.[57] (Fig. 1).

Ideally, aspirin desensitization should be performed after functional endoscopic sinus surgery (FESS). After FESS, aspirin desensitization has the most benefit compared with desensitization alone with regard to improved sense of smell, decreased nasal blockage, and decreased 22-item Sino-Nasal Outcome Test scores soon after surgery (a set of 22 nasal- and sinus-related symptoms graded from absent to severe).[56] This reflects the recognition that long-term aspirin desensitization does a better job in slowing the regrowth of hyper-

plastic sinus tissue and polyps rather than in inducing regression of established disease. In addition, because the infiltrating mast cells, basophils, and eosinophils, along with their adherent platelets, are a prominent source of the surge in CysLTs released after aspirin exposure, the severity of the reaction and extent of bronchospasm produced during aspirin desensitization will be attenuated by surgical removal of these tissues before performing desensitization. Also, many surgeons prefer performing surgery in patients who are not on daily aspirin, given the associated bleeding risk. As such, if desensitization does not produce a profound clinical result, then the daily aspirin will have to be discontinued before surgery can be performed, which necessitates a second desensitization procedure in short order. The optimal time to desensitize to aspirin is 2–4 weeks after nasal polypectomy before polypoid changes have had a chance to re-emerge.

As with the diagnostic challenge procedure, physicians should confirm stable asthma with a forced expiratory volume in 1 second that is within 10% of historical bests and ≥60% of predicted. The use of LT modifiers is essential to minimize the risk of bronchospasm associated with this procedure, in contrast to diagnostic challenge in which use of LT modifiers can mask the ability to recognize sensitization. In addition to LT receptor antagonists, many physicians also recommend premedicating with zileuton before and throughout the desensitization. Although they do not prevent reactions to aspirin, oral steroids administered before and throughout the procedure should also be considered to optimize baseline respiratory status. Antihistamines are generally avoided because, by blocking LTs and providing steroids, it should be possible to prevent or at least greatly ameliorate all lower respiratory symptoms and thereby still allow histamine-associated upper respiratory symptoms to be evident.[40,61] The presence of these upper respiratory symptoms will give the clinician more confidence regarding the diagnosis of AERD (if a diagnostic challenge was not first performed). A typical desensitization protocol is provided in Table 3. The standard starting dose of aspirin after desensitization is 650 mg twice daily, although the beneficial dose can be anywhere between 325 and 1350 mg daily.[60,62]

Aspirin desensitization does not produce tolerance. This is important to recognize because patients who are desensitized need to remain on aspirin indefinitely to retain their desensitized state. If the drug is stopped for longer than 48 hours, then the patient should not resume taking aspirin because he or she is at risk for a reaction; therefore, the patient should contact his or her physician for a repeated desensitization. It is important to keep in mind that adverse effects to aspirin desensitization are fairly common. In fact, results of studies showed that adverse effects can occur in almost a fourth of all patients who have this procedure.[59] Therefore, there is a high rate of patients who will stop taking aspirin in the long term due to non-compliance or treatment complications such as urticaria; tinnitus; and gastrointestinal symptoms, including gastric ulcers.[63,64]

SURGERY

Before desensitization, patients with AERD have often undergone multiple surgical interventions to remove polyps and to address the hyperplastic sinus tissue. In his original description of the "triad," Samter reported that surgery alone is ineffective in AERD.[5] Subsequently, in 1996, Stevenson et al.[65] described long-term outcomes for AERD treatment and confirmed that surgery alone is not curative. Mendelsohn et al.[66] reported similar poor outcomes regarding nasal polyposis with management that included surgery in isolation. In this study, 37% of patients required a revision surgery at 5 years and a staggering 89% required a revision surgery at 10 years.[66] However, surgical management is an essential adjunct to management of the upper airway component of this disease.[67] As discussed, aspirin desensitization is primarily effective in slowing the recurrence of hyperplastic sinus tissue and NPs, and is unlikely to regress established disease.

Aspirin desensitization in conjunction with FESS reduced the need for revision polypectomy from an average of once every 3 years, before aspirin desensitization, to once every 10 years during long-term therapy with aspirin.[68,69] Insofar as nasal sinus irrigation, often with concomitant corticosteroids, can be an essential component of medical management of CRSwNPs, surgery is often essential to allow access of the irrigant into the sinus cavities, and, again, the hyperplastic sinus tissue is a "source" for the surge in CysLTs that occurs with the desensitization procedure (a "leukotrienectomy" of sorts), so removing the tissue first allows for a more agreeable desensitization.[65] In summary, AERD cannot be cured with surgery, nor can it be properly medically managed without surgery. The ideal management for a patient with AERD remains a comanagement approach between allergy/immunology and otolaryngology specialists to provide personalized and optimal care.

ON THE HORIZON

There are no current studies that specifically used monoclonal antibodies for AERD; however, analysis of data of these medications' proven efficacy in patients with asthma and allergy and in patients with asthma and without allergy indicates potential efficacy in AERD. Omalizumab is an anti-IgE monoclonal antibody that is beneficial to patients with moderate-to-severe allergic asthma and in some nonallergic conditions (*e.g.,* chronic idiopathic urticaria and nonallergic asthma).[70,71] In a small study, omalizumab was given to 21 patients with AERD in whom it lowered the urinary concentrations of LTE_4 and PGD_2, which indicated inhibition of mast cell and eosinophil activation. In the same study, asthma exacerbations and hospitalizations were decreased, and symptom improvement was reported.[72] In another study that used omalizumab to treat CRSwNP, significant improvements in symptoms and NP size were observed, and, although not specifically analyzed for the presence of AERD, this condition was likely present in some of the subjects.[73] The obvious difficulty for clinicians in prescribing omalizumab for AERD remains that many patients with AERD have no evidence of specific IgE sensitization, which makes it nearly impossible to obtain approval when considering current insurance guidelines for this medication. The problem is amplified because many patients with AERD may have high levels of total IgE, yet no evidence of specific allergen sensitization, which makes it all the more frustrating for clinicians.[74]

Mepolizumab is an anti–interleukin (IL) 5 antibody that prevents eosinophil hematopoiesis and promotes eosinophil apoptosis, which thereby leads to rapid and profound reductions of blood and tissue eosinophil numbers.[75] In patients with CRSwNP, mepolizumab induced a reduction in NP size and symptom improvement.[76] Again, although not specifically analyzed for the presence of AERD, AERD was likely present in some of these patients. A competing anti–IL-5 antibody, reslizumab, was studied in patients with asthma and demonstrated significant amelioration of asthma symptoms and improvement in quality of life primarily in the subset of patients who also had NPs, which perhaps indicates an impact in the subset of patients with AERD.[77,78] Benralizumab is an antibody that binds to the IL-5 receptor and inhibits engagement by IL-5 and, in contrast to the anti-IL-5 antibodies, will also cause eosinophil, as well as basophil, destruction through antibody-dependent cell-mediated cytotoxicity.[79,80] As with the anti-IL-5 antibodies, benralizumab is effective in patients with eosinophilic asthma, yet, again, specific efficacy in those with AERD was not addressed.[80,81] Given the particularly robust expression of eosinophils, patients with AERD seem to have a phenotype in which intervention with IL-5 targeting therapies is particularly inviting, but specific studies are needed to confirm efficacy in this population.

Other drugs that are being developed for asthma, including those that target IL-4, IL-13, and thymic stromal lymphopoeitin, also encourage investigation into the AERD phenotype.[82] For example, dupilumab, an anti–IL-4R antibody that blocks activity of both IL-4 and IL-13 was recently demonstrated to have clinical efficacy in a pilot study in patients with CRSwNP.[83,84] In addition to its more general role in driving T-helper type 2 inflammation, TSLP is suspected in driving mast cell overproduction of PGD_2 and, as such, may play a role in the constitutive overexpression and rapid release of PGD_2 during aspirin-induced reactions.[85] The PGD_2 receptor CRTH2 (CD294) is expressed on T-helper type 2 cells, innate lymphoid type 2 cells, eosinophils, and basophils, and promotes their recruitment and survival. Most importantly, PGD_2 directly stimulates cytokine release from these cells.[86–88] These antagonists are undergoing clinical development in asthma; however, they have yet to be evaluated in AERD.[85]

CONCLUSION

AERD typically presents in adulthood and is clinically characterized by severe chronic rhinosinusitis, nasal polyposis, severe persistent asthma, and sensitivity to aspirin and other NSAIDs. Exposure to these agents results in a reaction that can include rhinitis, laryngospasm, and asthma exacerbations. Diagnosis is essential both to prevent potentially life-threatening reactions to these agents and also to define patients who may uniquely respond to AERD-specific therapies. Carrying out challenge with graduated aspirin dosing is the standard diagnostic modality for aspirin sensitivity, although graded nasal provocation testing with ketorolac may be equally sensitive and pose much-less risk. In patients in whom medical management of their CRSwNP or asthma failed, as is typical in this disease, and, with strong clinical suspicion based on a compelling history of symptoms that develop after more than one exposure or, alternatively, when challenge testing is positive, aspirin desensitization can prove extremely beneficial.

FESS and polypectomy ideally should be performed by an experienced otolaryngologist before desensitization. In addition to aspirin desensitization, LT modifiers and, in particular, the 5-LO inhibitors can also improve symptoms. Many biologics in development show promise in eosinophilic airway disease, and, although not specifically studied in AERD, given the profound intensity of eosinophilia in this disorder, it is likely that this phenotype defines a cohort in whom these agents should prove especially effective. Omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, anti-TSLP, and the PGD_2 (CRTH2) antagonists are all potential pharmacologic options that welcome further investigation in this disorder.

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