The role of aspirin desensitization in the management of aspirin-exacerbated respiratory disease

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Purpose of review
Aspirin-exacerbated respiratory disease (AERD) is a progressive inflammatory disease of the upper and lower airways characterized by marked eosinophilic nasal polyposis, asthma, and respiratory reactions to medications that inhibit the cyclooxygenase pathway. Aspirin desensitization has proven to be an effective tool in the management of this disease when used in a multidisciplinary setting. The purpose of this article is to review the current literature regarding AERD, aspirin desensitization, and share our opinion regarding the most optimal multidisciplinary approach to these complex patients.

Recent findings
Numerous studies, including randomized, double-blind, placebo-controlled trials, have demonstrated the therapeutic effectiveness of aspirin desensitization with significant improvement in number of sinus infections per year, olfactory scores, nasal symptom scores, asthma symptom scores, sinus operations, hospitalizations, emergency room visits, and oral steroid use. Furthermore, the role of surgery is becoming increasingly important for recalcitrant sinus disease with recent studies showing comprehensive surgery as more beneficial to disease management.

Summary
Aspirin desensitization is an effective therapeutic tool in the management of AERD. A multidisciplinary approach is critical between the otorhinolaryngologist and allergist to provide the most optimal care for this complex patient population.

Keywords
AERD, aspirin desensitization, aspirin-exacerbated respiratory disease, sinus surgery

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD), formerly known as Samter's triad, is a progressive inflammatory disease of the upper and lower airways that is characterized by eosinophilic sinusitis with marked nasal polyposis, asthma, and respiratory reactions to medications that inhibit cyclooxygenase 1 (COX-1). Alcohol-induced symptoms also occur in 75% of AERD patients [1]. It is reported to have a prevalence of 0.6–2.5% and occurs in 40% of patients who develop adult-onset asthma and chronic sinusitis with nasal polyps (CRSwNP). Seven percent of asthmatic patients have AERD and that prevalence increases to 15% in severe asthmatic patients [2]. The disease is considered progressive with a peak onset at 30–34 years of age and is more common in women. The syndrome often begins with flu-like symptoms which progress to chronic rhinosinusitis, symptoms of asthma, and ultimately to respiratory reactions to aspirin and nonsteroidal anti-inflammatory medications (NSAIDs) [3,4]. Patients often report dependency on corticosteroids to stabilize disease with 39–51% of AERD patients taking oral corticosteroids at a mean equivalent of 8 mg of prednisone. Twenty-four percent have required intravenous steroids in the preceding year

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KEY POINTS

- AERD is a progressive inflammatory disease of the upper and lower airways that is characterized by eosinophilic sinusitis with marked nasal polyposis, asthma, and respiratory reactions to medications that inhibit COX-1.
- Aspirin desensitization is a safe and effective tool in the management of AERD in which six RCTs have demonstrated effectiveness.
- Complete sinus surgery prior to desensitization improves outcome.
- A multidisciplinary approach is critical between the otorhinolaryngologist and allergist to provide the most optimal care for this complex patient population.

[3]. The severity of sinus disease is considerable with aggressive nasal polyposis. Reports including intracranial extension and otologic manifestations have been published in the literature [5,6]. As such, surgical intervention is undergone significantly more often in AERD patients with one study reporting 10 times as many sinus surgeries when compared with non-AERD patients [7].

The underlying pathogenesis of AERD is not completely understood but abnormal arachidonic acid metabolism appears to play a role. Abnormal metabolism results in increased leukotriene LTE_4 and baseline proinflammatory prostaglandin PGD_2. Decreases are noted in anti-inflammatory prostaglandin PGE_2 and lipoxins [8]. At the cellular level, a robust eosinophilic infiltrate is noted with the presence of mast cells and platelet-leukocyte aggregates. Platelet-leukocyte aggregates contribute more than half of the LTC_4 synthase activity of peripheral blood granulocytes resulting in an augmented generation of LTC_4 levels in patients with AERD [9]. Steinke *et al.* [10] have demonstrated the important role of interferon-γ (IFN-γ) in AERD. IFN-γ was found to be the most abundant cytokine in the profiling of AERD, which also includes a significant contribution from interleukin-4 (IL-4). Furthermore, IFN-γ robustly promoted eosinophil degranulation and increased the expression of genes involved in cysteinyl leukotriene synthesis. Unlike chronic hyperplastic eosinophilic sinusitis (CHES), which is primarily T helper type lymphocyte (TH)2, AERD appears to be a mixed TH1/TH2 disorder [10]. Diagnosis is suspected when clinical history is compatible with AERD, but aspirin challenges are required to confirm diagnosis. No current biomarkers demonstrate sufficient sensitivity and specificity to independently confirm a diagnosis of AERD [11].

DIETARY MODIFICATION AND MEDICAL THERAPY

In spite of avoidance of selective COX-1 inhibitors, respiratory inflammation persists in patients with AERD. Dietary salicylates have been found to be a potential source of clinically relevant exposure leading to exacerbation of airway inflammation [12]. Major dietary sources of salicylates are found in alcoholic beverages (22%), herbs and spices (17%), fruits (16%), fruit juices (13%), tomato-based sauces (12%), and vegetables (9%) [13]. Sommer *et al.* [14▪] performed a randomized, single-blind, controlled trial to evaluate the effects of a 6-week low-salicylate diet on quality of life and sino-nasal inflammation. When compared with baseline, patients were found to have significant improvement in multiple quality-of-life metrics [22-item sinonasal outcome test (SNOT-22), Nasal Sinus Symptom Scale (NSSS), and 7-item Asthma Control Questionnaire (ACQ-7)]. Additionally, improvements were seen in physician-rated endoscopy metrics [14▪]. Although a low-salicylate diet remains an inexpensive adjunctive treatment option for AERD patients with potential benefit, it is an onerous regimen to follow. Additional, preferably double-blinded, studies are needed with longer follow-up to determine the longitudinal stability and impact of dietary modification.

Given the overproduction of leukotrienes in AERD, leukotriene-modifying agents such as the leukotriene receptor antagonist, montelukast, and the 5-lipooxygenase inhibitor, zileuton, have been found to be effective in AERD symptom management. In a double-blind, placebo-controlled trial, montelukast was shown to improve lung function, reduce bronchodilator use, reduce asthma exacerbations, and improve quality of life [15]. Nasal symptoms and tissue eosinophilia were also found to improve after montelukast therapy in a prospective study [16]. Zileuton per patient report was found to be more effective for symptom control than montelukast in patients with AERD [17]. However, zileuton is not prescribed as often because of potential concern for liver toxicity and recommended transaminase monitoring when on therapy. Omalizumab, an anti-IgE monoclonal antibody, has shown early evidence of improvement of symptoms in AERD; however, the mechanism is less understood, as AERD is not considered an IgE-mediated disease [18]. Johns and Laidlaw [19] demonstrated that patients with AERD tend to have elevated baseline IgE levels possibly explaining the efficacy of omalizumab.

ASPIRIN DESENSITIZATION

Although medical therapy is the cornerstone of management of AERD, the refractory nature of the

disease necessitates adjunctive intervention to help optimize clinical outcome. Aspirin desensitization is a safe and effective tool in the management of AERD. Initially trialed in 1979, numerous studies have since demonstrated therapeutic efficacy of aspirin desensitization. Observational and retrospective studies have shown statistically significant improvement in the number of sinus infections per year, olfactory scores, nasal symptom scores, asthma symptom scores, sinus operations, hospitalizations, and emergency room visits [20]. Additionally, reduction of daily prednisone by nearly 70% is reported on average after therapy [4]. To date, seven randomized controlled trials (RCTs) have been performed investigating outcomes of aspirin desensitization with six of the trials demonstrating effectiveness [21▪▪,22–27]. The most recent study was a randomized, double-blind, placebo-controlled trial performed in 34 patients treated with 650 mg of aspirin twice daily for 6 months. Significant improvements were noted in FEV1, SNOT-22 score, symptom score, medication score, and Lund-Mackay computed tomography (CT) score [21▪▪]. One trial did not show effectiveness of treatment. Parikh and Scadding [24] did not detect clinical improvement; however, intranasal lysine-aspirin was only used.

The exact mechanism has yet to be delineated regarding the changes that occur after desensitization. Reported metabolic changes after aspirin desensitization include decreased levels and down-regulation of $CysLT_1$ receptors, inhibition of LTB_4 production, decrease in sputum IL-4, and attenuated secretion of LTE_4 [28–31]. The net result of these metabolic changes is a decrease in proinflammatory mediators and an increase in anti-inflammatory mediators.

Protocols for desensitization vary among institutions but generally begin with low-dose oral (p.o.) challenges of aspirin at 30 mg with escalation to 650 mg over a 2–3-day period depending on patient tolerance. One hybrid protocol that is gaining popularity uses intranasal ketorolac and a modified oral aspirin regimen and is usually completed in 2 days [32]. Although aspirin desensitization may be accomplished in an outpatient clinic, severe reactions may occur and therefore it is recommended that the facility be prepared to treat life-threatening respiratory and anaphylactic reactions including cardiovascular compromise [33]. Stevenson *et al.* attempted to define the optimal dose following desensitization in a cohort of 137 patients who had undergone successful aspirin desensitization. Patients were randomized into two clinical arms, one group treated with 325 mg of aspirin twice daily and the other group treated with 650 mg of aspirin twice daily. At 1 month, patients were offered a decrease or increase in dosage depending on their symptom severity and they continued that dose for 1 year. Both groups showed significant improvement in number of sinus infections, sense of smell, sinus symptoms, asthma symptoms, and hospitalizations. Interestingly, some patients randomized to 325 mg twice daily needed to increase to 650 mg twice daily for symptom control [23]. Therefore, although both dosages may be effective, each patient may need to adjust their maintenance dose to symptom severity. Common recommendations include initiating a patient's dose at 650 mg twice daily for a period of 3 months and then decreasing to a lower dose of 325 mg twice daily to determine if the patient can maintain satisfactory symptom control. Thus, the long-term dosage of aspirin that we recommend for control of AERD ranges from 325 mg to 1300 mg daily depending on the patient's response and tolerance. We prefer to start with the higher dose of 1300 mg daily and titrate downward slowly if the patient is well controlled or is intolerant to treatment at this high dose early on. Gastrointestinal intolerance is by far the limiting factor in using high dose aspirin therapy as up to 10% of patients on 650 mg twice daily will report gastric pain [33]. It is our experience that this symptom, when mild to moderate, can often be managed with various agents including proton pump inhibitors, sucralfate, misoprostol, or histamine-2 receptor antagonists.

Although aspirin desensitization can be successfully trialed in most patients with AERD, there is a subset of these patients who experience significant intolerance to desensitization due to severe cutaneous, gastrointestinal, or pulmonary symptoms. Laidlaw *et al.* attempted to investigate this subset of patients by stratifying AERD patients into those who tolerated desensitization and those who did not. Urinary and hematologic studies demonstrated that patients in the intolerant group displayed deregulated prostaglandin production, particularly to PGD_2, which showed dramatic increases. In this group, the production of PGD_2 correlated with severity of airflow obstruction during the clinical reaction [34]. It is difficult to predict which patients will have intolerance to desensitization. In general, this subgroup demonstrates substantially worse cutaneous and gastrointestinal symptoms, which may signal to the clinician a poor candidate for desensitization. In a similar matter, there is an additional, albeit small, subgroup of patients who obtain no symptomatic improvement from desensitization. In a retrospective review of 172 patients, 13% of patients received no improvement in symptoms after 1 year of

therapy [35]. In our experience, many of the aspirin 'nonresponders' often had concomitant perennial allergy or persistent infection which needed to be addressed in order to determine whether or not they were true aspirin responders.

SURGERY FOR ASPIRIN-EXACERBATED RESPIRATORY DISEASE

Surgical intervention followed by aspirin desensitization has proven to be an effective treatment regimen for AERD highlighting the importance of a multidisciplinary team consisting of an allergist and otorhinolaryngologist. Cho *et al.* [36] showed successful long lasting improvements in quality-of-life metrics in patients who underwent sinus surgery followed by aspirin desensitization for greater than 2 years. Due to severe sino-nasal disease burden, patients often require more extensive procedures. Early work by Jankowski *et al.* [37] and McFadden *et al.* [38] has shown that a more radical surgical approach is needed to control disease in AERD. Most recently, DeConde *et al.* [39▪] in their prospective, multi-institutional cohort analysis, demonstrated greater quality-of-life improvement in patients with AERD who undergo complete surgery rather than a more focused surgical approach. What defines 'complete' has yet to be determined. It is of the author's opinion that surgery performed for AERD should attempt to remove all polyp burden and provide wide-open sinus cavities to augment topical steroid therapy. This at minimum requires wide bilateral maxillary antrostomies, total sphenoethmoidectomies, and frontal sinusotomies. All residual bony partitions should be removed and the skull base skeletonized. Extended frontal sinusotomy, also known as the endoscopic modified-Lothrop procedure (Draf III), should be considered for recalcitrant frontal sinusitis. In this procedure, a common frontal neo-ostium is created allowing increased penetration of topical steroid therapy and improved control of sino-nasal inflammation. Morrissey *et al.* [40▪] have shown superior outcomes in patients with AERD after extended frontal sinusotomy for recalcitrant frontal sinusitis. Timing of aspirin desensitization generally begins 3–6 weeks after surgery once the sinus cavities have healed and the patient has been transitioned to topical steroid therapy.

CONCLUSION

The management of AERD requires a multifaceted approach targeting a variety of mechanisms known to be critical for disease pathogenesis. Medical and possibly dietary management provide a foundation for initial therapy. Aspirin desensitization has been shown to be an effective therapeutic tool in the management of AERD in conjunction with surgery performed to augment topical steroid therapy. A multidisciplinary approach is critical between the otorhinolaryngologist and allergist to provide the most optimal care for this complex patient population.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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