The role of aspirin desensitization followed by oral aspirin therapy in managing patients with aspirin-exacerbated respiratory disease: A Work Group Report from the Rhinitis, Rhinosinusitis and Ocular Allergy Committee of the American Academy of Allergy, Asthma & Immunology

Whitney W. Stevens, MD, PhD,a Elina Jerschow, MD,b Alan P. Baptist, MD, MPH,c Larry Borish, MD,d John V. Bosso, MD,e Kathleen M. Buchheit, MD,f Katherine N. Cahill, MD,9 Paloma Campo, MD, b Seong H. Cho, MD, f Anjeni Keswani, MD, f Joshua M. Levy, MD, MPH, k Anil Nanda, MD, l,n Tanya M. Laidlaw, MD, f and Andrew A. White, MDn Chicago, Ill; Bronx, NY; Ann Arbor, Mich; Charlottesville, Va; Philadelphia, Pa; Boston, Mass; Nashville, Tenn; Málaga, Spain; Tampa, Fla; Washington, DC; Lewisville, Flower Mound, and Dallas, Tex; and San Diego, Calif

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Aspirin-exacerbated respiratory disease (AERD) is characterized by the clinical triad of chronic rhinosinusitis with nasal polyps, asthma, and an intolerance to medications that inhibit the cyclooxygenase-1 enzyme. Patients with AERD on average have more severe respiratory disease compared with patients with chronic rhinosinusitis with nasal polyps and/or asthma alone. Although patients with AERD traditionally develop significant upper and lower respiratory tract symptoms on ingestion of cyclooxygenase-1 inhibitors, most of these same patients report clinical benefit when desensitized to aspirin and maintained on daily aspirin therapy. This Work Group Report provides a comprehensive review of aspirin challenges, aspirin desensitizations, and maintenance aspirin therapy in patients with AERD. Identification of appropriate candidates, indications and contraindications, medical and surgical optimization strategies, protocols, medical management during the desensitization, and recommendations for maintenance aspirin therapy following desensitization are reviewed. Also included is a summary of studies evaluating the clinical efficacy of aspirin therapy after desensitization as well as a discussion on the possible cellular and molecular mechanisms explaining how this therapy provides unique benefit to patients with AERD. (J Allergy Clin Immunol 2021;147:827-44.)

Key words: Aspirin-exacerbated respiratory disease, AERD, NSAID-exacerbated respiratory disease, Samter triad, aspirin desensitization

Aspirin-exacerbated respiratory disease (AERD), also referred to as Widal syndrome, Samter triad, aspirin-sensitive asthma, aspirin-induced asthma, and nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease, is an acquired inflammatory syndrome that is characterized by the clinical triad of asthma, eosinophilic chronic rhinosinusitis with nasal polyps (CRSwNP), and the development of respiratory reactions following exposure to all cyclooxygenase (COX)-1 inhibitors including aspirin and other NSAIDs (Table I). AERD is characterized in part by a dysregulation in arachidonic acid metabolism leading to elevated levels of cysteinyl leukotrienes (CysLTs), reduced levels of prostaglandin E2 (PGE2), and elevated levels of prostaglandin D2 (PGD2). AERD is estimated to affect 7% to 15% of patients with asthma and 10% to 16% of patients with CRSwNP. However, the condition is probably underdiagnosed and is not readily recognized by most physicians.7

The delay in diagnosing AERD is not harmless. On average, patients with AERD tend to have more severe upper and lower respiratory tract disease when compared with aspirin-tolerant patients with CRSwNP with or without asthma.8 Standard medical treatment for AERD focuses on managing the upper and lower respiratory tract symptoms and can include the use of corticosteroids, leukotriene-modifying drugs (LTMDs), and biologics that target type 2 inflammatory cytokines.9 Functional endoscopic sinus surgery (FESS) is also used to debulk nasal polyps and improve topical penetration of saline or corticosteroids. Despite these medical and surgical interventions, patients with AERD tend to undergo repeated sinonasal surgeries and are more likely to be dependent on chronic or frequent oral corticosteroids to manage their disease.6,10,11 Overall, this contributes to increased health care costs as well as enhanced physical and emotional burden of patients with AERD and their families.

Aspirin therapy after desensitization (ATAD) is a unique therapeutic option that can be offered to patients with AERD. This treatment can result in improved quality of life, delayed nasal polyp regrowth, reduced need for additional sinus surgeries, and improved control of upper and lower respiratory tract symptoms.12-16 In this report, the clinical evidence supporting the use of aspirin desensitization followed by maintenance oral aspirin therapy in patients with AERD will be reviewed. Expanding on the European Academy of Allergy and Clinical Immunology article on the diagnosis and management of NSAID-exacerbated respiratory disease,17 this report will provide an in-depth discussion on medical and surgical indications, desensitization protocols, and oral aspirin maintenance regimens available and commonly used in the United States (Fig 1).

### EVIDENCE SUPPORTING THE BENEFITS OF ASPIRIN DESENSITIZATION FOLLOWED BY DAILY MAINTENANCE THERAPY IN AERD

#### Case reports and retrospective analyses

In 1922, the first aspirin desensitization was described in a 37-year-old woman with asthma and nasal polyps who noted...
worsening asthma symptoms following the ingestion of aspirin. In this report, the “desensitization to aspirin was attained very easily ... by administering infinitesimal doses [of aspirin] then progressively increasing them in a continuous fashion,” which then allowed the patient to tolerate subsequent doses of aspirin without complications. In the 1970s, this phenomenon was again described by Zeiss and Lockey in an asthmatic patient with nasal polyps who reacted during the first ...

**FIG 1.** Algorithm for evaluating patients for an aspirin desensitization followed by maintenance aspirin therapy.
<table>
<thead>
<tr>
<th>Study</th>
<th>Level of evidence</th>
<th>Study description</th>
<th>Study duration</th>
<th>No. enrolled / completed the study</th>
<th>Sinus surgery required before desensitization?</th>
<th>Daily maintenance oral aspirin dose</th>
<th>Overview of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumry et al, 1983</td>
<td>4</td>
<td>Prospective</td>
<td>2-12 mo</td>
<td>17 / 17</td>
<td>No</td>
<td>325-2600 mg</td>
<td>47% reported persistent sinonasal symptom improvement and tolerated daily aspirin</td>
</tr>
<tr>
<td>Sweet et al, 1990</td>
<td>4</td>
<td>Retrospective</td>
<td>32-102 mo</td>
<td>65 on aspirin therapy and 42 avoiding aspirin</td>
<td>No</td>
<td>325-2600 mg</td>
<td>54% (35 of 60 subjects) tolerated aspirin Subjects on ATAD had significantly fewer ED visits, reduced number of steroid bursts, improved nasal symptoms, and fewer sinus surgeries compared with subjects avoiding aspirin</td>
</tr>
<tr>
<td>Stevenson et al, 1996</td>
<td>4</td>
<td>Longitudinal</td>
<td>1-6 y</td>
<td>78 / 65</td>
<td>No</td>
<td>325-1950 mg</td>
<td>83% (65 of 78 subjects) tolerated aspirin Subjects on ATAD had fewer sinus surgeries, reduced oral/intranasal steroid use, and improved sense of smell compared with before their ATAD</td>
</tr>
<tr>
<td>Berges-Gimeno et al, 2003</td>
<td>4</td>
<td>Longitudinal</td>
<td>4 wk</td>
<td>38 / 38</td>
<td>No</td>
<td>1300 mg</td>
<td>Subjects on ATAD reported improved nasal and asthma symptoms and reduced oral steroid use when compared with before their ATAD</td>
</tr>
<tr>
<td>Berges-Gimeno et al, 2003</td>
<td>4</td>
<td>Longitudinal</td>
<td>1-5 y</td>
<td>172 / 126</td>
<td>No</td>
<td>1300 mg</td>
<td>67% (115 of 172 subjects) tolerated aspirin and reported improved sinonasal and asthma symptoms, reduced steroid use, reduced number of sinus surgeries, and decreased ED visits for asthma compared with before their ATAD</td>
</tr>
<tr>
<td>Lee et al, 2007</td>
<td>4</td>
<td>Longitudinal</td>
<td>1 y</td>
<td>137 / 105</td>
<td>No</td>
<td>650-1300 mg</td>
<td>Both doses of aspirin were associated with improvement in nasal and asthma symptoms, reduced hospitalizations for asthma, and reduced need for sinus surgery. However, some patients on the lower dose required an increase to 1300 mg daily to see improvement</td>
</tr>
<tr>
<td>Rozsusi et al, 2008</td>
<td>4</td>
<td>Prospective</td>
<td>12 mo</td>
<td>14 / 14</td>
<td>No</td>
<td>100 mg</td>
<td>100% of subjects had recurrent nasal polyps and had no improvement in sense of smell or lung function</td>
</tr>
<tr>
<td>Havel et al, 2013</td>
<td>4</td>
<td>Retrospective</td>
<td>18-84 mo</td>
<td>51 on aspirin therapy and 33 avoiding aspirin</td>
<td>Yes (4-6 wk prior)</td>
<td>500 mg</td>
<td>Subjects on ATAD had less polyp regrowth and reported sinonasal and/or asthma symptom improvement compared with subjects avoiding aspirin</td>
</tr>
<tr>
<td>Comert et al, 2013</td>
<td>4</td>
<td>Prospective</td>
<td>3 y</td>
<td>40 / 18</td>
<td>No</td>
<td>300 mg</td>
<td>Subjects on ATAD had reduced systemic steroid bursts, fewer sinus surgeries, and noted improvement in some sinonasal symptoms compared with before their ATAD</td>
</tr>
</tbody>
</table>

(Continued)
challenge to aspirin but not on the following day when given another dose of aspirin as part of a double-blind double-dummy protocol.

These early studies indicated that patients could tolerate aspirin following desensitization but did not comment further on the course of their asthma or sinonasal disease. In 1980, Stevenson et al. published a report in which 2 patients with AERD remained desensitized on a daily aspirin regimen for several months and reported improvement in their clinical symptoms over the same time period. One patient was able to significantly reduce her dose of daily oral corticosteroids while the other patient reported improved nasal congestion, reduced asthma flares, and discontinuation of oral corticosteroids altogether. This work suggested that desensitizing patients with AERD and continuing them on daily aspirin had therapeutic benefits. One limitation of these early seminal studies was the small sample size including as few as 1 to 2 patients each.

Subsequent observational studies have examined larger cohorts of patients with AERD who were desensitized and maintained on daily aspirin for weeks, months, or years. (Table II). Patients reported subjective improvement in upper and lower respiratory tract symptoms and objective reductions in daily oral steroid requirements as early as 4 weeks following desensitization while on maintenance therapy. Even 10 years following desensitization, 85% of patients with AERD still taking daily aspirin found the therapy to be very or extremely helpful in controlling their sinonasal and asthma symptoms and in improving their quality of life. In this study, fewer patients with AERD on daily aspirin (32%) required an additional sinus surgery compared with those patients with AERD who discontinued the therapy (79%), but aspirin therapy did not significantly reduce the total number of sinus surgeries needed nor did it delay the time of the next sinus surgery between the 2 groups. In a separate study, 95% of patients with AERD who had sustained endoscopic and symptomatic improvement when sinus surgery was combined with aspirin desensitization/maintenance therapy and the latter treatment provided additional significant benefit to what was already observed from surgery alone. Furthermore, daily aspirin therapy was found to be effective at slowing the rate of polyp regrowth and reducing the need for repeat sinus surgery.

As with all therapies, aspirin desensitization followed by maintenance aspirin will not uniformly benefit all patients with

### Table II (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of evidence</th>
<th>Study description</th>
<th>Study duration</th>
<th>No. enrolled/completed the study</th>
<th>Sinus surgery required before desensitization?</th>
<th>Daily maintenance oral aspirin dose</th>
<th>Overview of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho et al, 2014</td>
<td>4 Retrospective</td>
<td>6 mo</td>
<td>28 / 21</td>
<td>Yes (4-6 wk prior)</td>
<td>650-975 mg</td>
<td>95% (20 of 21 subjects) tolerated aspirin Subjects reported a further improvement in sinonasal symptoms on ATAD than what they noted after sinus surgery</td>
<td></td>
</tr>
<tr>
<td>Adappu et al, 2018</td>
<td>4 Retrospective</td>
<td>30 mo</td>
<td>32 / 32</td>
<td>Yes (3-6 wk prior)</td>
<td>325-1300 mg</td>
<td>84% (27 of 32 subjects) tolerated aspirin Subjects reported a further improvement in sinonasal symptoms on ATAD than what they noted after sinus surgery</td>
<td></td>
</tr>
<tr>
<td>Jerschow et al, 2017</td>
<td>4 Prospective</td>
<td>4 wk</td>
<td>39 / 39</td>
<td>No</td>
<td>1300 mg</td>
<td>31% (12 of 39 subjects) had improved symptoms and lung function on ATAD 49% (19 of 39 subjects) could not complete the desensitization or had worsening symptoms and lung function on ATAD</td>
<td></td>
</tr>
<tr>
<td>Walters et al, 2018</td>
<td>4 Retrospective</td>
<td>10 y</td>
<td>92 / 57</td>
<td>No</td>
<td>325-650 mg</td>
<td>85% of subjects on ATAD reported that this treatment was very or extremely helpful in controlling their airway disease and improving their quality of life</td>
<td></td>
</tr>
<tr>
<td>Shah et al, 2019</td>
<td>4 Prospective</td>
<td>6 mo</td>
<td>40 / 40</td>
<td>Yes</td>
<td>1300 mg for the first 4 wk, then 650 mg</td>
<td>19 subjects who benefited from and 21 subjects who failed ATAD with a distant history of ESS were identified 24 of these 40 patients required subsequent ESS and underwent another ATAD 3-4 wk after repeat ESS. 100% (24 patients) tolerated this ATAD</td>
<td></td>
</tr>
</tbody>
</table>

ED, Emergency department; ESS, endoscopic sinus surgery.

*Level of evidence: 1 (systematic review of randomized trials or n-of-1 trials); 2 (randomized trial or observational study with dramatic effect); 3 (nonrandomized controlled cohort/follow-up study); 4 (case series, case-control studies, or historically controlled studies).
AERD. In a 5-year follow-up of desensitized patients with AERD at a large tertiary care center, 67% reported a subjective improvement with aspirin therapy, with 22% of the patients reporting either no improvement in their symptoms or discontinuing aspirin because of adverse side effects. If patients who experienced adverse reactions were excluded from analysis, 78% of patients with AERD reported improvement in clinical symptoms. In a 10-year survey from the same institution,

### TABLE III. Summary of double-blind placebo-controlled studies evaluating the clinical efficacy of ATAD in patients with AERD

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of evidence*</th>
<th>Study description</th>
<th>Study duration</th>
<th>No. enrolled / completed the study</th>
<th>Sinus surgery required before desensitization?</th>
<th>Daily maintenance oral aspirin dose</th>
<th>Overview of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stevenson et al, 1984</td>
<td>3</td>
<td>Double-blind placebo-controlled cross-over</td>
<td>7 mo</td>
<td>38 / 25</td>
<td>No</td>
<td>325 mg</td>
<td>57% (4 of 7 subjects) reported sinonosal and/or asthma symptom improvement and tolerated daily aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1300 mg</td>
<td>60% (3 of 5 subjects) reported sinonosal and/or asthma symptom improvement and tolerated daily aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2600 mg</td>
<td>69% (9 of 13 subjects) reported sinonosal and/or asthma symptom improvement and tolerated daily aspirin</td>
</tr>
<tr>
<td>Fruth et al, 2013</td>
<td>2</td>
<td>Double-blind placebo-controlled</td>
<td>36 mo</td>
<td>70 / 31</td>
<td>Yes (6 wk prior)</td>
<td>100 mg</td>
<td>Subjects on ATAD reported improved quality of life compared with controls, but there was no significant difference in rate of nasal polyp regrowth or size</td>
</tr>
<tr>
<td>Swierczynska-Krepa et al, 2014</td>
<td>2</td>
<td>Double-blind placebo-controlled</td>
<td>6 mo</td>
<td>20 / 15</td>
<td>No</td>
<td>624 mg</td>
<td>Subjects on ATAD reported improved asthma control, improved sinonasal symptoms, and reduced doses of inhaled steroids compared with placebo</td>
</tr>
<tr>
<td>Esmaeilzadeh et al, 2015</td>
<td>2</td>
<td>Double-blind placebo-controlled</td>
<td>6 mo</td>
<td>34 / 32</td>
<td>No</td>
<td>650-1300 mg</td>
<td>Subjects on ATAD had improvement in lung function, improved sinonasal symptoms, and reported less medication use compared with placebo</td>
</tr>
<tr>
<td>Mortazavi et al, 2017</td>
<td>2</td>
<td>Double-blind placebo-controlled</td>
<td>6 mo</td>
<td>41 / 38</td>
<td>No</td>
<td>1300 mg for the first 4 wk, then 650 mg daily for 5 mo</td>
<td>Subjects on ATAD reduced symptoms, improved FEV1, and improved quality of life compared with placebo</td>
</tr>
<tr>
<td>Chu et al, 2019</td>
<td>1</td>
<td>Meta-analysis</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>In patients with AERD, aspirin desensitization reduced symptoms of rhinosinusitis and improved quality of life. Adverse event rates were higher than in the placebo arm</td>
</tr>
</tbody>
</table>

*Level of evidence: 1 (systematic review of randomized trials or n-of-1 trials); 2 (randomized trial or observational study with dramatic effect); 3 (nonrandomized controlled cohort/follow-up study); 4 (case series, case-control studies, or historically controlled studies).
38% of patients with AERD reported discontinuing aspirin treatment predominantly because of adverse reactions (26%), a lack of clinical benefit (26%), or a need to undergo a surgical procedure (23%). Of the remaining 62% of patients who continued daily aspirin therapy, the vast majority reported significant clinical benefit. Some patients have worsening of respiratory symptoms (measured by respiratory questionnaires) and decline in FEV₁ while on high-dose aspirin treatment.

Double-blind placebo-controlled studies

Double-blind placebo-controlled studies remain the criterion standard for evaluating the safety and efficacy of a proposed therapy. However, such studies are inherently difficult to perform in patients with AERD. Although the precise mechanism of benefit from aspirin therapy is unclear, the effects of PGD₂ and CysLTs are dominant components. During an aspirin desensitization, urinary levels of PGD₂ further increase but later decrease while on high-dose aspirin therapy. In contrast, urinary levels of CysLTs have not been found to decrease while on high-dose aspirin therapy, but expression of the CysLT receptor 1 (CysLTR1) has been shown to be reduced.

Proposed mechanisms for clinical benefit

The cellular and molecular mechanisms driving the improvement following aspirin desensitization/maintenance therapy remain largely speculative (Fig 2). One of the central features of AERD is the high constitutive production of CysLTs and their overall disease control while on maintenance aspirin therapy compared with placebo. The first double-blind placebo-controlled cross-over study of aspirin in AERD was performed in the early 1980s. Patients were challenged to aspirin, then desensitized, and maintained on aspirin (or placebo) for 3 months. Following this, they underwent a 1-month wash-out period, were then re-desensitized, and assigned to the other treatment category for another 3 months. Of the patients who completed the study, 67% noted improvement in nasal symptoms and 48% noted improved asthma symptoms while on aspirin. Finally, a more recent double-blind placebo-controlled study compared 20 desensitized patients with AERD who were assigned to daily aspirin maintenance therapy or placebo for 6 months. Patients with AERD on aspirin reported subjective improvements in sinonasal and asthma symptoms (including smell) and a reduction in inhaled corticosteroid dose when compared with patients with AERD on placebo. Taken together, these studies highlight the utility of aspirin desensitization followed by daily maintenance therapy as a unique treatment option for patients with AERD.
further surge following ingestion of aspirin and other nonselective inhibitors of the COX-1 enzyme. This observation might suggest that therapeutic efficacy would be associated with modulation of CysLT concentrations. However, studies have consistently shown that aspirin desensitization is not associated with decreases in CysLT concentrations.4,42,43 Cahill et al44 paradoxically found increased levels of urinary LTE4 in patients with AERD taking high-dose aspirin therapy for 8 weeks.44 In contrast, desensitization is associated with decreased expression of the CysLT1 receptor,45 and an approximately 20-fold reduction in sensitivity to inhaled LTE4 is observed following desensitization.46 It is reasonable to consider that decreased expression of the LTE4 receptor could be a central mechanism of desensitization, although this concept has not been explored. Similarly, the mechanisms by which aspirin therapy modulates CysLT receptor expression are not immediately apparent.

There are also studies demonstrating off-target (COX-independent) mechanisms of aspirin, including those demonstrating its ability to inhibit signaling pathways (eg, Stat6) and expression of cytokines (eg, IL-4 and IL-13) that have been linked to upregulation of CysLT receptors.40-54 Although plausible, many of these studies used pharmacologically excessive concentrations of aspirin, leading to uncertainty of the biological significance. Aspirin maintenance therapy has also been associated with increased numbers of circulating eosinophils and basophils, suggesting that these inflammatory cells may no longer be recruited into the tissue to exert their inflammatory effects.33,44,55 However, patients receiving aspirin therapy who developed worsening respiratory symptoms and FEV1 decline had a significantly greater increase in peripheral eosinophil numbers.53

An alternative explanation for why aspirin desensitization/maintenance therapy is beneficial in AERD is that aspirin would act through its primary biological pathway (ie, inhibiting COX and downstream prostanoids) to block the recruitment and activation of inflammatory cells. PGD2 has been extensively studied in AERD. It is the primary prostanoid secreted by mast cells, but in AERD, it may also be produced by eosinophils.56 PGD2 acts through 3 distinct receptors, all of which are overexpressed in AERD to induce vasodilatation, recruit type 2 immune cells, and elicit bronchospasm. PGD2 concentrations are elevated in AERD, further increase on desensitization, and then markedly diminish during maintenance aspirin therapy.3,48,59 The increase in PGD2 during the desensitization may account for the clinical symptoms observed, whereas the reduced levels of PGD2 on maintenance therapy may account for reduced inflammatory cell infiltrate, type 2 cytokine concentrations, and reduced expression of CysLT receptors.

In addition to elevated levels of CysLTs and PGD2, AERD is characterized by increased levels of thromboxane A2,5 reduced levels and function of PGE2,60 downregulation of the PGE2 receptor, EP2,61,62 and increased numbers of platelet-adherent leukocytes.57 Although outside the scope of this report, each of these observations may serve as potential targets by which aspirin desensitization/maintenance therapy could mediate its effects. Future studies are thus warranted to further investigate the dysregulated arachidonic acid metabolism observed in AERD and how aspirin desensitization/maintenance therapy may provide clinical benefit.

**INDICATIONS FOR ASPIRIN DESENSITIZATION AND THERAPY**

Indications for initiation of a desensitization followed by maintenance therapy include rapidly recurring nasal polyps following sinus surgery, uncontrolled rhinosinusitis despite use of standard medical therapies, and the need for frequent bursts of systemic corticosteroids to control respiratory or sinus symptoms. Importantly, this therapy should only be recommended for patients with AERD because no clinical benefit has been described for aspirin-tolerant patients with CRSwNP and/or asthma.4 As such, it is essential to confirm the diagnosis of AERD before desensitization. Although the criterion standard for diagnosing AERD is a formal aspirin challenge, the diagnosis is more commonly made clinically. For patients with known physician-diagnosed asthma, documented nasal polyps, and a clearly-reported history of a respiratory reaction after ingestion of an NSAID, the diagnosis of AERD does not need to be confirmed by a formal aspirin challenge.

However, the presence or absence of NSAID reactions cannot always be established on the basis of patient-report alone. Up to 15% of patients with AERD are not able to identify whether or not they are intolerant to NSAIDs.64 Many of these patients actually report that they have taken NSAIDs without noting any hypersensitivity reactions—these patients do not become aware of their hypersensitivity until a physician-administered provocation challenge induces a reaction.65,66 As such, there are subsets of patients for whom a provocative aspirin challenge is required to determine proper diagnosis, and these patients usually fall into 1 of 4 categories:

1. **Patients who have not used NSAIDs recently.** Patients who have not used any NSAIDs recently, or have not used NSAIDs since the development of their nasal polyps or respiratory disease, may not know whether they are hypersensitive.

2. **Patients who are on a leukotriene-modifying drug.** The use of the leukotriene receptor antagonist montelukast, or the 5-lipoxygenase inhibitor zileuton, can in some instances pharmacologically blunt or sufficiently prevent the clinical manifestations of NSAID-induced reactions so that the reactions are not noticed by the patient.66,67

3. **Patients who are less perceptive to their reactions.** There are patients with AERD who present with both asthma and severe nasal polyps, but report that they can use aspirin or NSAIDs without adverse effects. For such patients who chronically live with complete nasal obstruction, intermittent episodes of worsened nasal congestion (as seen in the setting of NSAID ingestion) may go unnoticed. Patients with AERD also tend to underestimate the severity of their disease, and their perception of disease burden is in stark contrast to that of their providers.68 Therefore, a physician-observed provocative challenge may be required.

4. **Patients already on daily low-dose aspirin.** Patients with AERD who were already taking 81 mg aspirin for cardiovascular or cerebrovascular protection at the time of initial clinical evaluation may not report symptoms of NSAID-induced hypersensitivity. These patients tend to have very mild baseline asthma symptoms, and tolerate their current low-dose aspirin, but after stopping low-dose aspirin for at least 10 days, do develop aspirin-induced respiratory symptoms during a provocative oral aspirin challenge.69 The initial tolerance of low-dose aspirin may be
TABLE IV. Indications and contraindications for an aspirin desensitization and aspirin therapy in patients with AERD

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent sinonasal and asthma symptoms in a patient with AERD despite conventional medical and surgical therapy</td>
<td>Poorly controlled asthma</td>
</tr>
<tr>
<td></td>
<td>Significant nasal polyp burden at time of desensitization</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>History of eosinophilic esophagitis</td>
</tr>
<tr>
<td></td>
<td>History of gastric and/or peptic ulcer disease</td>
</tr>
<tr>
<td></td>
<td>History of a bleeding disorder or coagulopathy</td>
</tr>
<tr>
<td></td>
<td>History of medication nonadherence</td>
</tr>
<tr>
<td>Relative contraindication</td>
<td>History of anaphylaxis to aspirin or other NSAID*</td>
</tr>
</tbody>
</table>

*Patients with a history of anaphylaxis to aspirin or other NSAID may undergo an aspirin desensitization and aspirin therapy, but this decision merits careful discussion with the patient and physician.

because the aspirin-induced symptoms on initiation of low-dose aspirin were mild enough that they went unnoticed by the patient, or because they had started low-dose aspirin before the development of their respiratory disease.

CONTRAINDICATIONS FOR DESENSITIZATION AND INITIATION OF HIGH-DOSE ASPIRIN THERAPY

Most contraindications to ATAD are relative or temporary but should be considered when evaluating patients with AERD for therapy (Table IV).

Planned sinus surgery

Given the potential for increased intraoperative bleeding and associated decrease in intraoperative visualization accompanying NSAID use, it is advisable to delay aspirin desensitization until the completion of planned sinus surgery. In addition, the reactions to aspirin are also generally less severe when the desensitization is performed following sinus surgery. Although controlled studies are lacking, general expert consensus suggests that long-term clinical outcomes are improved when the initiation of aspirin therapy occurs after sinus surgery. Therefore, whenever possible and appropriate, it is often recommended that a sinus surgery to debulk the inflammatory nasal polyp tissue precede aspirin desensitization.

Pregnancy

Studies suggest that low-dose aspirin is safe to use in second and third trimesters. Low-dose aspirin may be prescribed for prevention of miscarriage in the first trimester and for prevention of preeclampsia. Generally, the use of aspirin doses above 81 mg daily in pregnant patients should be avoided because it may contribute to maternal and fetal bleeding and premature closure of the ductus arteriosus. Therefore, it is advisable to defer aspirin desensitization and/or discontinue aspirin treatment in patients who are pregnant.

Gastric ulcers or history of gastrointestinal bleeding

Patients with a history of gastric or peptic ulcers or with active ulcers should not initiate aspirin therapy before consulting a gastroenterologist. If their gastroenterologist confirms that aspirin treatment would be safe, these patients can be desensitized and aspirin treatment started. Current guidelines suggest that in patients with history of bleeding ulcers associated with low-dose aspirin, initiation of low-dose aspirin treatment for secondary prevention of cardiovascular disease is advisable but daily proton-pump inhibitors (PPIs) are recommended. Because there is limited evidence for aspirin therapy in patients with AERD with a history of gastric ulcers, the decision should be made on a case-by-case basis in consultation with the treating gastroenterologist.

Bleeding disorders and coagulopathies

Patients who have a history of bleeding disorders or coagulopathies (including deep venous thrombosis and pulmonary embolism) and/or who are currently receiving anticoagulation therapy should first discuss aspirin desensitization and maintenance therapy with their physician who manages their anticoagulation therapy.

Uncontrolled asthma

Patients with poorly controlled and symptomatic asthma should not undergo aspirin desensitization until asthma control is optimized.

Eosinophilic esophagitis

Patients with a history of eosinophilic esophagitis might be at risk for worsening gastrointestinal symptoms on initiation of aspirin therapy. Although evidence is lacking, it is possible that some of these patients may tolerate aspirin therapy if concomitantly treated with agents targeting IL-5 or IL-4/13.

SPECIAL CONSIDERATIONS IN SPECIFIC PATIENT POPULATIONS

Pediatric patients

AERD occurs infrequently in patients younger than 20 years. There is a concern for Reye syndrome in children with viral infections and salicylate use. Reye syndrome has several peaks of incidence around the ages of 1, 5, and 13 years. Thus, it is advisable not to treat patients younger than 14 years with aspirin. Aspirin treatment in children older than 14 years should be decided on a case-by-case basis with the intention of preventing polyp recurrence.

Elderly patients

Most of the aspirin desensitization and treatment outcome studies included patients younger than 70 years. Although at least 1 study included patients with AERD up to 81 years of age, the presence of comorbid conditions in the elderly that may be contraindications to aspirin therapy warrant further study. The use of biological therapies may be considered as alternative treatment options for disease control in older patients, although data for biologics in advanced age are also lacking.
Black and Latino patients

In a recent study of 39 patients, black and Latino patients were more likely than white patients to fail to tolerate the initial aspirin desensitization due to persistent bronchospasm or persistent gastrointestinal symptoms (nausea and vomiting). They were also more likely to have worsening upper and lower respiratory tract symptoms that continued for several weeks after initiation of high-dose aspirin. ATAD should still be offered to these patients, but additional counseling may be appropriate for these specific patient populations.

COST CONSIDERATIONS

An economic analysis of outpatient ATAD found that it was a cost-effective therapy for patients with moderate to severe AERD, even after accounting for the initial cost of the aspirin desensitization procedure. Compared with the estimated annual costs of biological agents conservatively ranging from $31,000 to $39,000, aspirin is an inexpensive treatment that is beneficial for many patients with AERD.

MANAGEMENT BEFORE ASPIRIN DESENSITIZATION

Medical management

Aspirin desensitization is a procedure that will often induce symptoms that mimic allergic reactions affecting the upper and lower airways. Therefore, before aspirin desensitization, it is recommended that all coexisting cardiopulmonary conditions be optimized. This is especially true regarding asthma given lung function can sharply decline and lower respiratory tract symptoms can worsen during the procedure. Although there are no randomized trials to support requisite spirometric values, most authors recommend a prebronchodilator FEV\(_1\) percent predicted value of at least 70% to safely perform desensitizations. In addition, sinonasal and asthma symptoms should be optimally controlled for the week before desensitization. There are several medical options that can be considered to ensure a patient’s upper and lower respiratory tract symptoms are appropriately managed before desensitization as follows.

Leukotriene-modifying drugs

It is recommended that all patients take standard doses of either a leukotriene receptor antagonist (LTRA) or 5-lipoxygenase (5-LO) inhibitor for approximately 3 days before and then during the aspirin desensitization. These medications typically do not completely eliminate the aspirin-induced reaction, but rather decrease lower airway symptoms (eg, wheezing, shortness of breath, and decrease in FEV\(_1\)\(_1\)) while preserving upper airway symptoms (eg, rhinorrhea and conjunctivitis). In rare cases, the use of an LTMD will completely block both upper and lower airway symptoms during a desensitization as discussed in the Approach to silent desensitizations section below.

Few trials have attempted to determine differences of an LTRA as compared with a 5-LO inhibitor in the attenuation of lower airway symptoms. In an observational study, an LTRA was found to be superior to a 5-LO inhibitor (zileuton), and another small study of 6 subjects found that zileuton had minimal effects in 4 of 6 subjects. There is also limited data on the effects of combining a 5-LO inhibitor with an LTRA before desensitization. LTMDs serve as an important component of the medical management of patients with AERD, particularly before aspirin desensitization.

Corticosteroids

Inhaled corticosteroids (ICSs) and ICSs combined with long-acting β\(_2\)-agonists for asthma should be continued during aspirin desensitization. These medications have a less pronounced effect as an LTMD because they can shift the aspirin-induced reaction from the lower to the upper airway. If a patient is already on ICSs with stable disease, they should be continued at the same dose before and throughout the protocol. If a patient has well-controlled asthma and does not routinely take ICSs, the added benefit of starting an ICS before the desensitization is unclear. Likewise, the benefit of starting systemic corticosteroids in a patient who is not chronically dependent and whose asthma is controlled is also unknown. However, select patients with poorly controlled asthma may need a short course of oral corticosteroids to improve asthma control before desensitization. There is little data on the use of intranasal corticosteroids during oral aspirin desensitization, though many practitioners continue their use.

Antihistamines

The use of histamine 1 receptor antagonists before aspirin desensitization is controversial. Some authors have advocated that they be discontinued before challenge and desensitization because they may blunt a reaction to aspirin and potentially mask the sentinel reaction during the procedure. In contrast, others have performed aspirin desensitization while continuing antihistamines, especially in shorter desensitization protocols.

Biologics

Biologic therapy for asthma (eg, mAbs against IgE, IL-4 receptor alpha [IL-4R\(_\alpha\)], IL-5, and IL-5 receptor alpha [IL-5R\(_\alpha\)]) may also decrease both upper and lower airway symptoms during the desensitization. One randomized controlled trial of 11 subjects found that after use of omalizumab for 16 weeks, 70% of subjects randomized to the intervention arm had neither upper nor lower respiratory tract symptoms during aspirin desensitization, as compared with 0% of subjects randomized to the placebo arm. The mechanism may be related to decreased mast cell activation and decreased PGD\(_2\) and CysLT levels. Standard practice is to continue biologics during the procedure if needed for asthma control, with the understanding that aspirin-induced reactions may be blunted or not occur.

Consideration can also be given to biologic therapy as pretreatment for patients who have previously failed aspirin desensitization due to frequent or severe reactions, though this requires further research.

Surgical management

Endoscopic sinus surgery is often completed before desensitization. Although this historically was done because of the universal prevalence of nasal polyps and the relative contraindication of surgery while taking high-dose aspirin, there is emerging evidence for the improved safety and tolerance of aspirin desensitization when preceded by FESS. In a prospective observational trial, Jerschow et al compared aspirin-induced reaction severity among subjects undergoing repeated aspirin desensitizations before and 3 and 4 weeks after FESS. Among this
cohort of 28 subjects, all demonstrated decreased severity of clinical reactions following FESS. Strikingly, despite having positive reactions preoperatively, 43% of these patients developed no symptoms during the postoperative aspirin desensitization. These findings were validated in a separate retrospective study by Huang et al11 who reported a decreased risk of significant airway reactions following sinus surgery (odds ratio, 9; P = .033).

Patients with AERD are more likely to receive complete FESS.96 This is likely related to the extent of inflammatory polyp burden and the relatively high rate of surgical failure among patients with AERD.97,98 Given the emerging evidence of decreased reaction severity associated with postoperative aspirin desensitization, complete FESS with debulking of inflammatory polyp burden should be considered before desensitization in any surgically naive patient or those with significant polyp burden.

SELECTING A LOCATION FOR AN ASPIRIN DESENSITIZATION

Aspirin desensitization protocols can be safely performed in an outpatient setting for most patients with AERD. The outpatient setting is generally recommended as appropriate for patients who have well-controlled asthma, a baseline FEV₁ greater than or equal to 70% of predicted (and >1.5 L absolute), are not currently using an oral beta-receptor blocker, and do not have any underlying comorbidities that would make management of severe reaction symptoms more difficult.99,102,103 Patients with very stable asthma despite an FEV₁ less than 70% could be considered for a desensitization on a case-by-case basis. In addition, in select cases, increased caution and access to inpatient-level care may be preferred, including for patients with poorly controlled asthma or hemodynamic instability. The outpatient setting may also be appropriate for patients who are not able to stop oral beta-blockers, because this may heighten the risk of severe anaphylaxis during reactions due to the poor response to rescue medications such as epinephrine although the clinical significance of this can be variable.101

Although earlier guidelines had recommended that a peripheral intravenous (IV) line be placed before provocative aspirin challenge procedures,102,103 currently available safety data are strong enough that at most major academic centers in the United States that routinely perform aspirin provocation tests, they are done without a peripheral line in place. However, some practitioners continue to place an IV line before the procedure especially in the event that severe gastrointestinal upset and vomiting occur, so that IV rescue medications can be used.

ASPIRIN DESENSITIZATION PROTOCOLS

There are several published aspirin challenge and desensitization protocols for patients with AERD, with variations in dose escalation time (60 minutes, 90 minutes, 3 hours), starting dose (20.25 mg, 40.5 mg), and route of provocative drug administration (oral aspirin, intranasal ketorolac, intranasal lysine-aspirin).79,99,103-108 Although inhalational and IV aspirin desensitizations are performed at a few European and Asian sites, these modalities generally require the administration of nasal lysine-aspirin, which is not approved for use in the United States.102,109-111 The most common US protocols involve orally administered ketorolac and orally administered aspirin and will be the focus of this report (Table V).

Two-day oral aspirin desensitization protocol

One of the earliest publications to describe an oral aspirin desensitization suggested a 2-day procedure that required a dosing interval of 3 hours.46 Commercially available 81-mg aspirin tablets can be cut with a pill cutter and used as the first dose, 40.5 mg. Doses are given at 3-hour intervals up to 325 mg (day 1: 40.5 mg, 81 mg, 162 mg, then 3 hours of observation before discharge; day 2: 325 mg). Placebo can be used on the first day of challenge, especially for those patients who are particularly anxious and there is concern for a false-positive reaction to the procedure.

Two-day intranasal ketorolac + oral aspirin desensitization protocol

In this protocol,109 parenteral ketorolac (Toradol) is diluted in saline and administered intranasally. Ketorolac solution is made by mixing ketorolac 60 mg/2 mL with 2.75 mL of normal saline. The solution is placed in a meter-dose nasal spray bottle such that each spray delivers 0.1 mL and 1.26 mg of ketorolac. The intervals between the ketorolac doses are 30 minutes. One spray in 1 nostril (1.26 mg), 1 spray in both nostrils (2.52 mg), 2 sprays in both nostrils (5.04 mg), and 3 sprays in both nostrils (7.56 mg) are given. After 60 minutes, 60-mg aspirin tablets are given twice with a 90-minute observation period between doses. After the second 60-mg dose, the patient is observed for 3 hours before discharge. The next day, 150 mg and then 325 mg of aspirin are administered with either a 90-minute or 3-hour interval, with another 3-hour observation period following the last oral aspirin dose before discharge.

The pros of the intranasal ketorolac protocol are that it has an excellent safety profile including increasing the percentage of patients who develop only naso-ocular reactions during the desensitization.109 Cons for this protocol include more limited access to parenteral ketorolac and metered-dose nasal spray bottles when compared with availability of oral aspirin.

One-day aspirin desensitization protocols

Two recent publications from academic medical centers in the United States have highlighted the safety and efficacy of completing an aspirin desensitization with oral aspirin in a single day.92,99 For both protocols, the procedure begins with 40 to 40.5 mg of oral aspirin, and proceeds with increasing doses of 81 mg, 162 mg, and then 325 mg of oral aspirin every 60 to 90 minutes. The main difference between these 2 protocols is the form of aspirin used. In the 60-minute protocol, dissolved tablets of Alka-Seltzer in solution are used,99 whereas in the 90-minute protocol, aspirin tablets are cut using a pill cutter to achieve the desired lower doses of aspirin.112 The predissolved nature of the aspirin in the Alka-Seltzer solution may allow for faster absorption112 and may decrease the time from provocative dose to reaction, therefore shortening the overall length of the procedure.

Regardless of the protocol, there is now general agreement that the desensitization can end with a maximum final dose of 325 mg, because patients are expected to display symptoms of reaction by this point and can tolerate higher doses without additional symptoms.81 In addition, patients who react at 162 mg or less
During the 2-day desensitization protocol rarely react again at 325 mg, and consideration can be given to administer this dose at home. In terms of the starting dose for 1-day oral aspirin protocols, studies report that patients rarely react to very low oral aspirin doses, suggesting that it is appropriate and safe in most circumstances to begin these challenges at a dose of 40.5 mg. Most patients react after receiving the highest dose (7.56 mg) of intranasal ketorolac (and sometimes even at lower doses), and so it is not recommended to start with higher doses when following the intranasal ketorolac protocol. Before escalating to the next dose of medication within any desensitization protocol, the patient should be clinically evaluated by physical examination and vital signs as well as lung function should be measured by spirometry or peak expiratory flow readings. Monitoring peak nasal inspiratory flow can also be an informative assessment of the upper airways.

### EXPECTED REACTIONS DURING A DESENSITIZATION

By definition, patients with AERD should become symptomatic during an aspirin desensitization. AERD is confirmed if they develop clinical symptoms and/or have a decrease in FEV$_1$ by more than 15% and/or a reduction in peak nasal inspiratory flow by more than 20%. Reactions typically are observed between 60 and 80 mg of aspirin but this differs on an individual basis.

Typically, patients will develop a combination of the following upper respiratory tract symptoms: nasal congestion, rhinorrhea, postnasal drip, sneezing, nasal, ocular, or aural pruritus, conjunctival injection, and lacrimation. Reactions are typically self-limited within 3 to 4 hours of symptom onset. Lower respiratory tract symptoms include cough, shortness of breath, and wheezing. As noted previously, clinically significant declines in FEV$_1$ of 20% or more were observed in 37% of patients with AERD despite being on concurrent montelukast therapy.

Patients may also develop cutaneous symptoms including flushing, urticaria, angioedema, and macular pruritic eruptions on the extremities. Gastrointestinal manifestations including dyspepsia, nausea, vomiting, diarrhea, and crampy abdominal pain are also associated with evidence of systemic mast cell activation and occur in 10% to 30% of cases depending on the desensitization protocol used. As with the respiratory symptoms, the severity of these symptoms varies widely from mild and transient to severe and persistent such that aspirin must be discontinued. Hypotension and laryngeal angioedema are rare, but physicians performing aspirin desensitizations need to be prepared to treat such events.

### TABLE V. Select aspirin desensitization protocols

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Oral aspirin and ketorolac</th>
<th>Oral aspirin</th>
<th>Oral aspirin</th>
<th>Oral aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>8:00 am</td>
<td>20-40 mg 1.26 mg ketorolac (1 spray)</td>
<td>20.25 mg</td>
<td>41 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td>8:30 am</td>
<td>2.52 mg ketorolac (2 sprays)</td>
<td>40.5 mg</td>
<td>81 mg</td>
<td>160 mg</td>
</tr>
<tr>
<td></td>
<td>9:00 am</td>
<td>5.04 mg ketorolac (4 sprays)</td>
<td>81 mg</td>
<td>161 mg</td>
<td>325 mg</td>
</tr>
<tr>
<td></td>
<td>9:30 am</td>
<td>7.56 mg ketorolac (6 sprays)</td>
<td>162.5 mg</td>
<td>325 mg</td>
<td>Desensitization complete*</td>
</tr>
<tr>
<td></td>
<td>10:00 am</td>
<td>160 mg</td>
<td>325 mg</td>
<td>Desensitization complete*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10:30 am</td>
<td>60 mg aspirin</td>
<td>Desensitization complete*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11:00 am</td>
<td>40-60 mg</td>
<td>60 mg aspirin</td>
<td>Instructions and discharge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11:30 am</td>
<td>60 mg aspirin</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12:00 pm</td>
<td>60 mg aspirin</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12:30 pm</td>
<td>60 mg aspirin</td>
<td>Desensitization complete*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:00 pm</td>
<td>60 mg aspirin</td>
<td>Desensitization complete*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:30 pm</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:00 pm</td>
<td>60-100 mg</td>
<td>Instructions and discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:30 pm</td>
<td>325 mg</td>
<td>Instructions and discharge</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>3:00 pm</td>
<td>Desensitization complete*</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>5:00 pm</td>
<td>Desensitization complete*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Actual time needed for the protocol to be completed may vary on the basis of severity of reaction and the time needed for recovery.

Factors that may predict the severity of aspirin-induced reactions

The severity of symptoms during an aspirin desensitization protocol vary widely from patient to patient. Unfortunately for treating clinicians, there are very few known factors that predict whether a patient will develop a clinically significant reaction or that predict the severity of reaction. Although the tests are not traditionally part of routine clinical evaluation, the degree of elevation of baseline LTE$_4$ and PGD$_2$ in the urine is known to be associated with the severity of respiratory reactions and the extent to which FEV$_1$ falls during aspirin-induced reactions. From a clinical standpoint, duration of challenge, the current state of the

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**Note**: The table above shows a desensitization protocol with two schedules: 2-d protocols and 1-d protocols. The protocol details include the time of day and the dose of aspirin and/or ketorolac to be administered. The protocol is designed to progressively increase the dose of aspirin until a desensitization is completed, with monitoring for symptoms and adverse reactions at each step.
Systemic reactions should be treated with intramuscular epinephrine, and very occasionally intravenous fluids are needed.

**Protocol Modifications for Aspirin-Induced Reactions**

Regardless of the protocol, after a clinical reaction has developed, the patient should be treated and observed for a 3-hour period to ensure complete resolution of symptoms. Following symptom resolution, the provocative dose of aspirin (or ketorolac) should be repeated before continuing with the next-higher dose during a desensitization. Most patients have achieved a desensitized state once they have tolerated both the repeated administration of the provocative dose and an additional higher dose without developing further symptoms.

**Aspirin Challenge Versus Aspirin Desensitization**

Aspirin challenges may be indicated to confirm whether a patient truly has AERD. Aspirin desensitizations are performed such that a patient may be started on daily maintenance aspirin therapy. The protocol used for either an aspirin challenge or a desensitization is the same. In addition, if the patient has AERD, it is expected that they will develop a clinical reaction during the procedure. Following the development of a reaction in both an aspirin challenge and desensitization, the patient should be treated and monitored for at least 3 hours until their symptoms have resolved. The important difference between a challenge and desensitization is what occurs after the patient’s clinical reaction has resolved. In a challenge, the protocol is discontinued and the patient is discharged. In a desensitization, the provocative aspirin dose is repeated and the protocol is continued through the 325-mg dose of aspirin as described above.

**Oral Aspirin Therapy Following Aspirin Desensitization**

**Maintenance of tolerance to aspirin**

Following aspirin desensitization, patients are cross-desensitized to nonselective COX inhibitors as long as they continue on aspirin 325 mg daily or higher doses. Patients can also change from one COX inhibitor to another without losing the desensitized state. If patients discontinue aspirin treatment, their NSAID tolerance may continue for several days. However, in one study, repeating intranasal aspirin-lysine challenges 24 hours after the initial challenge resulted in positive reactions in 98% of the patients. Therefore, if a desensitized patient misses more than 2 days of aspirin it is strongly recommended they be evaluated for repeat desensitization before resuming therapy.

**Dose of aspirin therapy**

After patients have been desensitized to aspirin, they should continue taking aspirin daily. A uniform consensus is lacking on the exact daily dose of aspirin that should be offered to the patients. However, several groups agree that the aspirin dose should be at least 300 mg and possibly 650 mg or 1300 mg of aspirin daily. It is recommended to start with aspirin 650 mg twice daily for 1 to 6 months. Patients who are doing well can then reduce the dose to 325 mg twice or once daily to see...
whether they maintain benefit. If symptoms worsen on 325 mg once or twice a day, it is then recommended to increase the dose back to 650 mg twice daily.26

For doses less than 325 mg twice daily, one study showed that dose reduction less than 325 mg twice daily led to recurrence of nasal congestion.30 Another study looking at 100 mg versus 300 mg daily showed no improvement in symptoms on the lower dose (100 mg daily) and recurrence of nasal polyposis. Subjects on 300 mg daily had decrease in nasal polyposis, and of 35 patients who continued taking 300 mg aspirin daily, none required a repeat sinus surgery during a median follow-up for 27 months.31 Therefore, doses of 300 mg of daily aspirin or greater may be helpful for sinonasal symptoms, but doses lower than 300 mg may not provide clinical benefit.31,32

Duration of aspirin treatment

It is recommended to attempt an initial trial period of 6 months on aspirin treatment to determine whether the patient notes clinical improvement. For patients who respond to aspirin, we recommend continuing aspirin indefinitely.14,123 For patients who show no signs of clinical benefit, high-dose aspirin may be discontinued after 6 months. However, the patient may elect to maintain aspirin tolerance by taking 325 mg of aspirin daily, be it for cardio-protection or freedom to use other NSAIDs as needed. Aspirin doses lower than 325 mg daily may not provide cross-tolerance to other NSAIDs.

Aspirin should be discontinued at any time if the patient is having significant side effects despite medical management. For those patients who discontinue aspirin therapy, they should immediately resume avoiding all COX-1 inhibitors. In these patients, alternative medical management options should be reviewed. In aggressive recurrent nasal polyposis, referral for an evaluation by a rhinologist should be considered. Antecedent endoscopic sinus surgery performed 3 to 4 weeks before desensitization improves aspirin treatment response in patients with AERD and may convert patients who failed initial aspirin treatment to a more responsive phenotype.29

Patients on aspirin therapy who require surgery are presented with 2 options. First, the aspirin can be completely discontinued 2 weeks before the procedure. In this situation, aspirin cannot be restarted after the procedure unless done with a desensitization. A second option is to lower the dose of aspirin to 325 mg once daily. Aspirin can then be held the day before the procedure and restarted in the evening after the procedure. This allows aspirin to be restarted within the 48-hour refractory period. The decision on which protocol to use is based on surgical considerations and is usually made by the surgeon. Many minor procedures such as a colonoscopy can be done on daily aspirin. A small case series suggests that stopping aspirin and bridging with ibuprofen might be another option to maintain desensitization but will limit the antiplatelet effect of aspirin.123

Currently, there are no data on alternative dose escalation protocols following aspirin withdrawal nor on safety regarding bleeding complications with this approach. Alternative approaches to this question merit further study.

Risks and side effects

There are a number of risks and side effects associated with maintenance aspirin therapy that can generally be mitigated with appropriate patient selection. Reports suggest that discontinuation of aspirin is frequently due to the gastrointestinal side effects, nasal or ear bleeding, and skin rash induced by aspirin.12,37 There are patients who discontinue aspirin treatment because of the lack of effectiveness or worsening of the upper or lower respiratory tract symptoms.33,125

Gastrointestinal toxicity is the most common reason for discontinuation of aspirin, most likely due to gastritis.12,37,125 Clinicians should ensure careful review of patient risk factors for gastroduodenal toxicity from aspirin/NSAIDs before initiating high-dose aspirin.126,127 For patients at a higher risk of gastrointestinal toxicity or those who develop gastrointestinal side effects after starting high-dose aspirin, adding a PPI or sucralfate can be beneficial.128,130 In patients with persistent gastrointestinal symptoms following aspirin desensitization on high-dose PPI, clinicians should consider whether or not they may benefit from an esophagogastroduodenoscopy.

Risk of bleeding has not specifically been studied in AERD.131 In the general population, bleeding secondary to aspirin most commonly occurs in the gastrointestinal tract. Aspirin is associated with approximately a 50% increased risk of gastrointestinal bleeding in patients on aspirin for primary prevention of cardiovascular disease.132,133 Intracerebral hemorrhage is very rare in the general population.134 In patients on aspirin for primary prevention of cardiovascular or cerebrovascular disease, the risk of hemorrhagic stroke is very low.135,136 However, studies examining the bleeding risk while taking high doses of aspirin are warranted.

Peripheral eosinophilia frequently occurs in patients with AERD on high-dose aspirin.137 Generally, patients are asymptomatic and can be monitored safely. Coronary artery vasospasm, a rare but clinically important side effect, has been described in patients with AERD before and following aspirin desensitization. Vasospasm is responsive to oral corticosteroids and is presumed to be eosinophil related.137 Esophageal eosinophilia has also been described after aspirin desensitization.77,138

Approach to silent desensitizations

A clinical dilemma can exist if a patient with an excellent history and sinonasal polyposis does not “react” during the desensitization despite the fact that clinical criteria for AERD are met. One strategy that is frequently used in a patient who undergoes a nonreactive challenge would be to assume that they do have AERD and experienced a “silent desensitization”139 related to the use of LTMDs during the desensitization or recent FESS. Subsequently, a trial of aspirin therapy would be initiated and if the patient responded well, aspirin would be continued. However, because multiple interventions are likely taking place at the same time, it may be very difficult to tell whether the patient truly has AERD by this method, and it is unknown whether to recommend that they remain on long-term high-dose aspirin. Certainly, it would be undesirable to have a patient without AERD continue on a treatment that has potential adverse effects without confirmation of true benefit.

An alternative approach to the patient with no symptoms during desensitization would be to have them return later for a full 1-dose 325 mg oral aspirin confirmatory challenge in a closely monitored and equipped outpatient setting with 3 hours of observation (Fig 1). Aspirin must be washed out for 2 weeks before rechallenge, and antihistamines, LTMDs, cromolyn, and ketotifen are held
for 7 days before this confirmatory challenge. Oral steroids are either discontinued or weaned down to the lowest dose needed to control the patient’s asthma. Once this occurs, patients who react to the open full-dose challenge are confirmed to have had a silent desensitization, whereas those who do not react (double-negatives) are truly not patients with AERD and will not obtain benefit from aspirin therapy nor do they need to be labeled as “NSAID allergic.”

**APPARTO TO DIFFICULT DESENSITIZATIONS**

Aspirin desensitization is widely regarded as safe. Yet, more difficult scenarios need to be prepared for in all situations. It is clear that the reaction to aspirin is systemic. In a large series of 167 consecutive desensitizations, 23 (13.7%) were classified as severe including having a gastrointestinal reaction, a decline in FEV₁ more than 30%, and/or requiring injectable epinephrine or 3 or more doses of β₂-agonist. Such patients can have reactions longer than anticipated and require a higher degree of nursing and physician attention during the desensitization.

In patients with a gastrointestinal reaction, the severity of these symptoms often eclipses the respiratory symptoms. Unfortunately, gastrointestinal reactions are not easy to abort. Treatment with histamine 1 receptor and histamine 2 receptor antagonists, ondansetron, and IV fluids should be considered. In a study of 45 patients with AERD undergoing aspirin desensitization or challenge, the addition of misoprostol during the procedure was not shown to reduce the intensity of overall symptoms. However, it is still possible that misoprostol may provide some clinical benefit in a select patient population and could be considered under certain circumstances but the side effects must be discussed with the patient before initiation. Injectable epinephrine may be required and should be considered in the treatment of moderate to severe gastrointestinal anaphylaxis. Of note, in a small study, recent endoscopic sinus surgery appears to lessen the severity of gastrointestinal symptoms during desensitization.

In patients with significant reactions, using a slower paced protocol could also successfully achieve full desensitization. Another subgroup of severe reactors manifests prominent laryngeal symptoms. The presentation includes shortness of breath, but stridor can frequently be heard over the pharynx. These patients may or may not have significant drops in FEV₁ and concomitant lower airway involvement. Although short-acting β₂-agonists can relieve bronchospasm, the addition of racemic epinephrine nebulization can abort the laryngeal symptoms.

Acute pancreatitis has been reported in several situations as an ensuing complication during or immediately following aspirin desensitization. This does present a problem in the acute setting of delineating a typical gastrointestinal reaction from the rare evolving pancreatitis. Yet, given the cases reported in the literature, in any patient with persistent epigastric pain or symptoms refractory to standard therapy, pancreatitis should be considered. The mechanism for this phenomenon is unknown.

**NEED OF FURTHER RESEARCH**

Although the clinical utility of ATAD in patients with AERD has been appreciated for decades, there remain many unanswered questions especially in regard to the mechanisms by which daily treatment with aspirin, but not other COX-1 inhibitors, provides clinical benefit. In addition, there are no clinically validated metrics that predict in advance which patients with AERD will respond best to ATAD. Furthermore, subphenotypes of AERD have been described, and further work is necessary to determine whether a particular phenotype (or endotype) may preferentially respond to ATAD. Finally, in the era of novel biologics being developed for asthma and CRSwNP, consensus is still needed among physicians as to when to initiate these therapeutics versus ATAD in the management of patients with AERD.

**Conclusions**

Since it was first described in the early 1980s, ATAD has held an unusual status in the field of allergy. It may be considered too risky to perform in some practices and at times has been controversial and obscure. It is unequivocal that patients with AERD represent some of the most severe asthmatic and nasal polyp sufferers. Both blinded and longitudinal studies consistently show benefit of ATAD, and there is a wide breadth of data and clinical experience on the safety of both the desensitization and the maintenance aspirin therapy. Although not all patients with AERD will respond, ATAD has the potential to improve upper and lower respiratory tract symptoms, prevent or delay sinus surgery, and enhance quality of life in most affected patients. Selecting the appropriate patient for aspirin desensitization/maintenance therapy is essential, and diagnostic aspirin challenges to confirm the diagnosis of AERD should be considered in patients with an uncertain clinical history. In addition, ATAD can be a highly economical treatment option when compared with both frequent sinus surgeries and the new array of biologics that are now available for nasal polyposis and severe type 2 asthma. In conclusion, aspirin desensitization followed by maintenance aspirin therapy is a unique treatment option that should be considered in all eligible patients with AERD as a means to improve clinical outcomes and delay or prevent future sinus surgery.

**REFERENCES**


93. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma, & Immunology, American College of Allergy, Asthma, & Immunology, Joint


Feldman M, Cryer B. Aspirin absorption rates and platelet inhibition times with 325-mg buffered aspirin tablets (chewed or swallowed intact) and with buffered aspirin solution. Am J Cardiol 1999;84:404-9.


