

Aspirin Therapy in AERD: “One Size” Might Not Fit All



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Aspirin-exacerbated respiratory disease (AERD), also referred to as nonsteroidal anti-inflammatory drug–exacerbated respiratory disease in other areas of the world, is a major contributor to the disease burden within the nasal polyposis and severe asthma populations. Patients are more likely to experience disease recurrence with medical and surgical treatment failure. In this issue, Laulajainen-Hongisto et al¹ address the efficacy of long-term aspirin treatment in patients with AERD. Aspirin treatment is recognized as an accepted therapeutic modality for AERD.² It contributes to better control of asthma, decrease in emergency room visits, decrease in systemic corticosteroid use, and a decreased burden of sinus surgeries for nasal polyps because it appears to attenuate nasal polyp regrowth.³

However, questions remain unanswered on the appropriate aspirin dose for treatment and on the timing of treatment initiation. One study showed that there was no significant difference in clinical response to aspirin doses of 325 mg once daily, 325 mg 4 times daily, or 650 mg 4 times daily. However, the authors suggested that higher doses were necessary to maintain clinical benefit, while at the same time advising on the need for further aspirin dosing studies.⁴ Reducing the daily dose from 1300 mg to 650 mg was possible in about 50% of patients without a loss of effectiveness.⁵ Another study⁶ showed no improvement in sinonasal symptoms at 100 mg daily aspirin dose and recurrence of nasal polyposis in all 7 patients after 1 year. Of 35 patients who were taking 300 mg aspirin daily, none required a repeat sinus surgery during a median follow-up for 27 months. Therefore, doses of at least 300 mg of daily aspirin could be helpful for preventing polyps but lower doses may not provide any clinical benefit.^{6,7}

The side effects and limitations of aspirin therapy are well known. In addition, the need to perform a desensitization to begin this treatment remains an impediment for some patients and practices. These factors make the implementation of aspirin therapy more challenging than some other therapies commonly

used in the management of nasal polyposis or severe asthma. As such, it is recognized that the utility of aspirin therapy might be different across diverse ethnic populations and health care delivery systems. Therefore, the real-world effectiveness as described by Laulajainen-Hongisto et al¹ is an important contribution and is worth reviewing.

The authors evaluated the records of 171 patients who were treated by a total of 7 ENTs or pulmonologists who routinely cared for patients with AERD. This was not a randomized trial; thus, the aspirin dose, timing of desensitization, and management of side effects were managed individually. The authors report a high rate of aspirin discontinuation in their AERD patient population (63%). Although at an unexpectedly low rate, 37% of the study patients continued aspirin treatment and did not have nasal polyp recurrence during the 5-year follow-up. This study highlights some significant data gaps in the utility of aspirin treatment after desensitization (ATAD) in AERD.

In this study,¹ the dose of aspirin was not uniform (322 mg; interquartile range, 50-1500 mg). It is possible that doses at 1300 mg daily are more likely to be associated with treatment benefit than doses lower than 300 mg. Dose escalation in those without clinical response might have identified more treatment responders. The timing of aspirin treatment initiation was not uniform and was significantly different between the groups (Table I of Laulajainen-Hongisto et al¹). Recent studies confirm that the polyp burden at the time of desensitization adds to the reaction severity, with most experts recommending that ATAD be started immediately following polypectomy.^{8,9} Although other studies finding benefit from ATAD also likely had variability in the timing of ATAD implementation, this remains an important aspect to consider.

The specifics of the surgical treatment are also important. In the present study, there seems to be an indication (although not significant) of a more complete sinus surgery being beneficial for ATAD in those who continued aspirin treatment (Table II of Laulajainen-Hongisto et al¹).

The authors report an unusually high rate of aspirin treatment discontinuation in their study—higher than has been previously reported. This included immediate failure (failure to desensitize), long-term side effects, and confounding medical issues (surgery, pregnancy, etc). Cahill et al¹⁰ reported that poorly suppressible prostaglandin D₂ during initial desensitization is associated with difficulty desensitizing and might represent a portion of this group. Difficulties to desensitize some of the patients with AERD were also noted in other cohorts.¹¹ Although this group is indeed difficult to desensitize, it can almost uniformly be done if the patient and the clinician commit to a several-day process. Once desensitized, in our experience, these patients do not appear to experience gastritis or gastrointestinal discomfort at any higher rate than the rest of the treated group. Long-term side

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effects, predominantly gastrointestinal side effects, are not unusual with aspirin treatment. Aspirin treatment was discontinued in 10% to 30% of the patients because of gastrointestinal side effects.^{3,12} Yet, a recent report of 109 patients with AERD who underwent sinus surgery followed by ATAD found that 0.92% had clinically significant gastrointestinal bleeding, 0.92% anaphylaxis, and 14% discontinuation due to minor side effects; 83.5% remained on aspirin therapy at the time of study report.¹³

This article also brings up the issue of ethnic/racial variability in response to aspirin therapy. The study group is a primarily Finnish population that might respond differently or have a higher side effect profile than other populations that show benefit.

With the advent of biologic therapies for eosinophilic asthma and nasal polyposis, the need to establish the place for inexpensive ATAD is more important. Defining the optimal timing post-operatively for implementation of ATAD as well as the optimal dose is important to study in a randomized deliberate manner. The issue of ethnic and racial differences in response to aspirin is critical to address as is the pressing need to identify biomarkers and other predictors of individual response to treatment to better identify a patient best suited for a specific therapy in AERD.

Designing a prospective double-blind placebo-controlled multisite trial on aspirin treatment in a diverse population of patients with AERD seems to be overdue and could help answering these questions. In the age of biologics, it becomes essential to focus on individual biomarkers predicting response to therapy.

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