

## Age as a factor in treatment of aspirin-exacerbated respiratory disease: relationship to required aspirin maintenance dose after desensitization

Aspirin-exacerbated respiratory disease (AERD) is an aggressive triad consisting of asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and sensitivity to aspirin (ASA) or cyclooxygenase-1 (COX-1) inhibitors. On the basis of a large institutional experience with AERD, we hypothesized that age may play a significant role in AERD disease severity and treatment.

Few studies have addressed the demographic-based differences in AERD symptom severity and treatment requirements. This discrepancy is evident in CRSwNP, where women have demonstrated a higher likelihood of oral corticosteroid use and required more revision sinus surgeries compared with men.<sup>1</sup> In females with AERD, perimenstrual asthma and increased sinus symptoms were more common during menstruation.<sup>2</sup> Although previous studies have demonstrated a female predominance in AERD, no previous studies have evaluated age-based differences in AERD severity.<sup>3,4</sup>

In our retrospective analysis, we included adult (>18 years old) patients with ASA-challenge-proven AERD, who underwent endoscopic sinus surgery (ESS) followed by aspirin desensitization (AD) between July 2016 and February 2019 at a tertiary care academic institution. Covariates for analysis were chosen *a priori*, including age and aspirin maintenance dose at 6 months. Six-month ASA maintenance dose was chosen as a surrogate metameter for AERD symptom severity. Participants were categorized by age into young adults (age 18-39 years,  $n = 28$ ), middle-aged adults (age 40-59 years,  $n = 43$ ), and older adults (age  $\geq 60$  years,  $n = 21$ ).<sup>5</sup> All included patients adhered to a standardized and previously reported ASA maintenance therapy protocol without consideration of age that included an initial dose of 650 mg twice daily with titration after 3 to 6 months to a minimum of 325 mg/day based on patient response and tolerance.<sup>6</sup> At 6 months post-AD, patients were generally on a stable daily ASA maintenance dose of between 325 mg and 1300 mg. Deidentified data were tabulated, and subsequent analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The cohort was stratified by age, and statistical analyses were performed to compare strata by surrogate

of disease severity. Continuous data were analyzed using nonparametric Kruskal-Wallis tests. All statistical testing was performed with a two-sided alpha level of 0.05.

Ninety-two patients with AERD met the inclusion criteria for this pilot study. The median age was 49.0 (interquartile range, 38.5-58.0) years, and females made up 64.1% of the cohort. The average daily ASA maintenance dose at 6 months was  $859.3 \pm 379.2$  mg. Stratification based on age demonstrated a significant reduction in ASA maintenance dose in the older adult cohort (age 18-39,  $928.6 \pm 372.3$  mg; age 40-59,  $907.0 \text{ mg} \pm 358.5$  mg; age  $\geq 60$ ,  $669.3 \text{ mg} \pm 384.5$  mg;  $p = 0.03$ ). The results of age-based analysis of AERD severity are presented in Table 1. The average preoperative 22-item Sino-Nasal Outcome Test (SNOT-22) scores among age-stratified cohorts were: age 18-39,  $33.2 \pm 22.9$ ; age 40-59,  $46.5 \pm 25.9$ ; age  $\geq 60$ :  $36.2 \pm 23.5$ ;  $p = 0.09$ . At 12-months post-AD, the SNOT-22 scores were no different statistically between age-stratified cohorts (age 18-39,  $16.0 \pm 16.6$ ; age 40-59,  $16.8 \pm 12.4$ ; age  $\geq 60$ ,  $15.0 \pm 9.7$ ;  $p = 0.92$ ), as shown in Table 2.

Previous studies have addressed the clinical characteristics of AERD, including time of onset, sex differences, use of medication, and patterns based on ethnicity.<sup>3,4,7</sup> No study has identified aspirin maintenance dose difference based on age. Our findings demonstrate that individuals with AERD >60 years of age require significantly lower doses of daily ASA for maintenance therapy at 6 months after desensitization.

Although management of AERD can consist of conservative measures, for instance COX-1 inhibitor avoidance, nutritional interventions, or leukotriene-modifying agents, the combination of ESS followed by AD is effective at controlling disease burden.<sup>8</sup> ESS results in decreased ASA sensitivity in AERD patients,<sup>9</sup> and AD is widely recommended to reduce the sinonasal manifestations associated with the disease.<sup>10</sup> We hope our findings will help classify AERD patients into different groups of severity based on age. Doing so could guide management of AERD patients during aspirin treatment after desensitization, with the possibility of adjusting the ASA dose based on age or predicting when patients may require an increase or a decrease in therapeutic interventions. Most importantly, our results suggest that, when initiating maintenance treatment, older adults (age  $\geq 60$  years) may be started at a lower ASA dose compared with those younger than age 60, with upward titration as needed based on symptoms.

Our pilot study showed a significant reduction in ASA maintenance dose in our AERD cohort >60 years of age. Given the retrospective nature of our study, there are inherent limitations to our study design, including selection

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**TABLE 1.** Aspirin maintenance dose by age

	Age 18-39 years (n = 28)	Age 40-59 years (n = 43)	Age ≥60 years (n = 21)	p value
ASA maintenance dose, mean (SD)	928.6 (372.3) mg	907.0 (358.5) mg	669.3 (384.5) mg	0.03

Abbreviations: ASA = aspirin; SD = standard deviation.

**TABLE 2.** Mean SNOT-22 scores by age

	Age 18-39 years (n = 24)	Age 40-59 years (n = 39)	Age ≥60 years (n = 18)	p value
Preoperative (SD)	33.2 (22.9)	46.5 (25.9)	36.2 (23.5)	.09
12-month post-AD (SD) <sup>a</sup>	16.0 (16.6)	16.8 (12.4)	15.0 (9.7)	.92

Abbreviations: AD = aspirin desensitization; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

<sup>a</sup>Total number of patients for each age-stratified cohort is n = 15 for 18-39 years, n = 26 for 40-59 years, and n = 12 for ≥60 years at 12-month post-AD

biases in the accrual of patients, recall biases on review, and nonresponse biases within study participants. Another limitation that could be argued is that the treating physicians may be biased toward using lower doses of ASA in the elderly due to risks of falls or bleeding. However, the prescribing allergist who administered AD at our institution adhered to a strict previously published initiation protocol that did not vary ASA dose according to age.<sup>6</sup> In addition, the SNOT-22 scores at 12 months post-AD were not significantly different among the 3 age groups which suggests that ASA titration in all age-stratified cohorts achieved the same clinical endpoints despite statistically lower dose requirements in the oldest cohort. Last, the results presented herein represent only a single institution's experience with AERD. The sample size is modest and may be underpowered to detect differences in AERD symptom severity. Future studies will include a prospective study aimed to better quantify the severity of AERD based on age. Despite


the limitations, we have presented early findings of lower symptom severity, based on a lower ASA maintenance dose, in older adults. Our findings warrant further investigation.

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