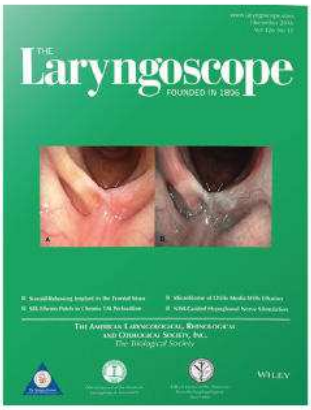
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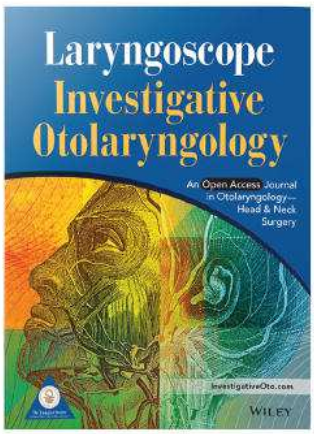


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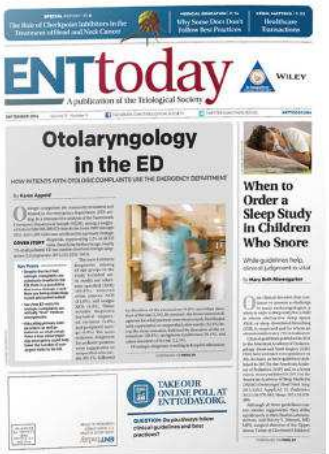


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Best Practice

Is Aspirin Desensitization Indicated for the Treatment Recalcitrant Chronic Rhinosinusitis With Nasal Polyposis in Aspirin-Exacerbated Respiratory Disease?

Joshua M. Levy, MD, MPH; Timothy L. Smith, MD, MPH

BACKGROUND

Chronic rhinosinusitis with nasal polyposis (CRSwNP) in aspirin-exacerbated respiratory disease (AERD) represents a severe chronic rhinosinusitis (CRS) phenotype with increased sinonasal inflammation and worse health-related quality-of-life (HRQoL) compared to CRSwNP without aspirin sensitivity. Conventional treatment strategies frequently fail to control this recalcitrant form of airway inflammation, with 37% of patients requiring revision endoscopic sinus surgery (ESS) within 5 years of their first procedure. Aspirin desensitization represents a treatment option for patients with AERD, with associated benefits extending beyond those seen with strict acetylsalicylic acid avoidance. However, broad utilization remains limited due to heterogeneous outcome studies, availability, and concerns of adverse reactions associated with long-term therapeutic daily aspirin therapy.

LITERATURE REVIEW

A high-quality systematic review (level 2a) of aspirin desensitization for the treatment of AERD was completed by Xu et al.,[1] with the identification of 11 studies published through February 2013. Significant improvements in nasal endoscopy are reported using several objective measures, as well as decreased rates of revision ESS, CRS exacerbations, and systemic corticosteroid utilization, with a maintenance dosage for daily aspirin therapy ranging from 100 mg once daily to 650 mg twice daily. Although significant improvements were demonstrated among all patients undergoing daily maintenance therapy, several studies noted improved disease control with high-dose aspirin protocols $\geq$300 mg daily. The majority of HRQoL measures were nonvalidated, with significant improvements in nasal symptom scores and reported olfaction with most studies reporting follow-up of >12 months. Adverse effects were reported by % to 23% of patients, with the most common reactions including cutaneous flushing, urticaria, and the rare report of gastrointestinal (GI) bleeding, epistaxis, and asthma exacerbation. Whereas an association between increasing aspirin dosage and adverse events was suggested, a statistically significant relationship was not demonstrated.

Several recently published randomized controlled trials (level 1b) further evaluate aspirin desensitization following revision ESS for patients with AERD. Świerczyńska-Krępa et al.[2] evaluated the effectiveness of aspirin desensitization among 20 patients with AERD versus 14 with CRSwNP and aspirin tolerant asthma (ATA). The Sino-Nasal Outcome Test was utilized to measure HRQoL, with significantly improved mean total scores among AERD patients through 6 months follow-up (P =.04), but not ATA or placebo controls. Patients with AERD expressed higher levels of inflammatory urinary leukotriene E_4 versus ATA (P <.007), without significant change following desensitization. No major adverse reactions were encountered, with 25% of patients failing to complete the study due to dyspepsia (n = 5). One patient with AERD developed a transient skin rash, but completed study participation.

Fruth et al.[3] evaluated adverse events associated with chronic low-dose, 100-mg-daily aspirin therapy following desensitization. Seventy patients with AERD were prospectively randomized into daily aspirin versus placebo control groups, with both cohorts undergoing desensitization 6 weeks following revision ESS. Patients were followed for 36 months following desensitization, with no adverse events reported. A high dropout rate of 55% was noted during follow-up, however, with similar

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rates among aspirin and placebo groups. Additional outcomes included objective measures of sinonasal inflammation and olfaction, with the validated Rhinosinusitis Disability Index (RSDI) to evaluate HRQoL. Patients receiving daily aspirin therapy following desensitization demonstrated a lower but statistically nonsignificant rate of polyp recurrence versus placebo (28% vs. 62%, P =.0785). However, Kaplan-Meier analysis of patients with polyp recurrence demonstrated a later onset and lower frequency of recurrent disease among patients taking daily aspirin. The aspirin group also reported significantly higher median RSDI scores versus placebo (68.6 vs. 46.0, P =.0324), without significant difference in olfactory function (P =.0748).

Economic modeling has evaluated the cost-effectiveness of aspirin desensitization for patients with AERD. Shaker et al.[4] (level 2b) constructed a hypothetical cohort of 30-year-old patients with AERD, with comparison of patients undergoing aspirin desensitization versus conventional medical therapies, including topical corticosteroids and leukotriene modification. Risk reductions and adverse event rates were estimated from the current literature, with abstraction of inpatient and ambulatory treatment costs from the Healthcare Cost and Utilization Project and a large North American healthcare plan, respectively. Ambulatory aspirin desensitization represents a cost-effective treatment for moderate to severe AERD, with an associated cost of $6,768 per quality-adjusted life year gained ($18.54 per additional symptom-free day). The cost-effectiveness of therapeutic desensitization remained robust across a wide array of assumptions, with increasing cost saving associated with higher severity of AERD.

The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis[5] (level 2a) recently evaluated the evidence basis in support of aspirin desensitization for CRSwNP in AERD, with a policy level recommendation for aspirin desensitization after ESS to prevent recurrent disease. Adverse events are associated with dosage of daily aspirin therapy, with GI irritation reported in <3% of patients undergoing low-dose, 100-mg protocols.

BEST PRACTICE

Aspirin desensitization is indicated for the treatment of CRSwNP in AERD following revision ESS. Desensitization is cost-effective, with several high-quality studies demonstrating improved disease control and HRQoL following desensitization, with <3% of patients experiencing minor adverse reactions with low-dose maintenance protocols. Further study is necessary to identify factors associated with successful desensitization, with determination of the most appropriate dosage of daily aspirin therapy.

LEVEL OF EVIDENCE

Two randomized controlled trials (level 1a), a systematic review (level 2a), an international consensus statement (level 2a) and an economic modeling of retrospectively collected data (level 2b) were evaluated in this review.

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