

An update on the epidemiology of aspirin-exacerbated respiratory disease

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ABSTRACT

Background: Aspirin-exacerbated respiratory disease (AERD) is a disorder of nasal polyposis, asthma, and hypersensitivity respiratory reactions when on systemic cyclooxygenase 1 blockade.

Methods: AERD warrants specific evaluation as an endotype of asthma and chronic sinus disease due to unique therapeutic opportunities. Currently, aspirin therapy is uniquely beneficial as an anti-inflammatory therapy in AERD, with multiple additional therapies currently in early to late clinical studies, which might also show exceptional benefit in AERD.

Results: Yet, given the lack of a simple diagnostic test, opportunities to identify patients with AERD are still frequently neglected.

Conclusion: Identifying the prevalence and population characteristics necessary to determine appropriate candidates in whom to perform diagnostic aspirin challenge remains critically important and was the purpose of this article.

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Aspirin-exacerbated respiratory disease (AERD) was initially described in 1922 by Widal *et al.*¹ but then disappeared from the medical literature for decades until redescribed by Samter and Beers² in 1968. At that point, numerous studies began to look at this and considered it primarily as a phenotype of severe asthma. Although traditionally considered to be an uncommon disorder, it is not entirely clear that the disease is truly rare, or perhaps has a higher prevalence, but is being missed by clinicians too busy or unaware to know exactly what to look for. To confuse things further, numerous and widely varied prevalence estimates emerged in the literature that attempted to define how common this disorder is.

AERD is a clinical triad of nasal polyposis, asthma, and respiratory hypersensitivity reactions on cyclooxygenase 1 (COX-1) inhibition. AERD is more commonly associated with severe asthma, recalcitrant nasal polyposis, and higher morbidity related to anosmia, systemic corticosteroid requirements, and quality of life.^{3–6} Thus, identifying this condition has an important role in counseling patients regarding their disease process and in providing additional medical options, *e.g.*, aspirin desensitization, to help control their respiratory inflammation.

Prevalence Study Limitations

Unfortunately, for many years, the widely different rates of prevalence reported for AERD clouded the literature with uncertainty. If AERD can reportedly be seen in between 1.2%⁷ and 44%⁸ of individuals with asthma, it is understandable that the clinician really has no idea how often to expect seeing this. Until 2015, the most comprehensive study to look at AERD prevalence in individuals with asthma concluded that it existed in 21% of adults with asthma and in 5% of pediatric patients with asthma.⁹ In the past decade, these statistics did not measure up to the clinical experience of many centers. AERD is very rare in children, with only scattered reports existing in the literature.¹⁰ Furthermore, to conclude that one in five children with asthma has AERD also is not consistent with many larger single studies that looked at prevalence. Therefore, two groups set out to

look again at this issue with careful attention to bias that may have affected previous studies.^{11,12} There are several issues that affect the prevalence estimates of AERD that are useful to discuss because they also impact the clinician when evaluating for AERD. Thus the need for diagnostic aspirin challenge, the influence of comorbid diseases, the effects of current controller medications, and regional or ethnic variability in AERD prevalence. Each of these issues will be addressed in detail, specifically in the context of clinical care and presentation of these patients.

Very few prevalence studies are performed by using diagnostic aspirin challenges. The reason for this is somewhat obvious, it is tremendously difficult to screen a large population in such a manner. Although aspirin challenges are safe, they can be time consuming and labor intensive if repeated spirometry is performed. Yet, this is the criterion standard of diagnosis in AERD, and any study that does not use this test is using a surrogate diagnostic marker with more limited sensitivity and specificity. For example, ~10 to 15% of subjects with a history of a nonsteroidal anti-inflammatory drug (NSAID) reaction in the past will have a negative aspirin challenge result in the clinic.¹³ Thus, the reaction history was likely inaccurate. In the largest natural history study of AERD performed to date, 15% of the subjects who exhibited a positive aspirin challenge result did not know that they had AERD before that challenge.¹⁴

Somewhat conveniently for study purposes, these numbers may cancel each other (15% think they have it but do not, and, conversely, 15% of the patients who do not know that they have it actually do), but, nonetheless, the importance of obtaining an accurate diagnosis cannot be overstated. Indeed, Morales *et al.*¹² note in their meta-analysis that the prevalence of AERD was similar in both challenge studies and reported patient histories. It is critical for the physician to realize that the absence of an NSAID reaction by history does not rule out the diagnosis of AERD. In any patient with severe eosinophilic airway disease for which the question of an AERD diagnosis remains uncertain, an NSAID challenge should be considered.

Studies evaluating AERD prevalence in subjects with asthma do not clarify the presence of nasal polyposis. Yet, it is clear that nasal polyposis is near universal in AERD, and an individual with asthma and without nasal polyposis is extremely unlikely to have AERD. Thus, prevalence estimates for AERD in all individuals with asthma will include a widely heterogeneous population, many of whom would never be expected to have AERD. This has ramifications for the clinic, where, in an individual patient, the presence of asthma and nasal polyposis can be easily and simultaneously assessed. For patients with asthma and without nasal polyposis, an AERD diagnosis can be excluded, and, for an individual with asthma and with nasal

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Table 1 Factors that affect the prevalence of aspirin-exacerbated respiratory disease

Decreased Prevalence	Increased Prevalence
Asthma without nasal polyps	Polyp recurrence by 6 mo after surgery
Intact sense of smell	High Lund-Mackay CT score
Remote history of single NSAID reaction	Alcohol intolerance (respiratory symptoms)
Noneosinophilic polyps (China)	Severe asthma
Nasal polyps without asthma	Hospitalization related to NSAID reaction
Childhood onset	More than two reactions to unrelated NSAIDs
Urticaria or cutaneous NSAID reaction only	Cutaneous and respiratory NSAID reaction

CT = Computed tomography; NSAID = nonsteroidal anti-inflammatory drug.

polyposis, the AERD might be identified in 30–40%, even in the absence of a clear NSAID reaction.¹⁵

In the decades since Samter and Beers² described AERD, the ability to control underlying asthma has changed dramatically. Prevalence studies in the 1970s need to be evaluated through the lens of poor baseline control and much higher markers of asthma severity. Thus, many “reactions” to aspirin might have been misinterpreted as secondary to COX-1 inhibition when these reactions might have been viral or spontaneous. This led researchers to advocate for the necessity of placebo challenges to identify baseline asthma stability. Thus, a patient with a remote history of an aspirin reaction 15–20 years ago might be recalling a period of poor baseline asthma control with a reaction that might have been falsely attributed to the NSAID. Conversely, leukotriene modifiers and omalizumab have both been shown to significantly modify the aspirin reaction.^{13,16–18} This could convert a patient who would have ended up in the emergency department with a severe aspirin-induced asthmatic reaction to a milder nasal-ocular reaction that is brushed off as “nothing” and ignored or never connected to the NSAID. This makes it more difficult to interpret challenge studies in patients on leukotriene modifier drugs because objective challenge outcomes for solitary nasal ocular reactions are not commonly used. The utility of adding peak nasal inspiratory flows and validated symptom score measurements have been described.^{19,20}

Finally, just as the diagnosis of AERD is contingent on the presence of nasal polyposis, it is also clear that the inflammatory process is highly eosinophilic in AERD.^{21–23} Although nasal polyposis has largely been shown to be eosinophilic, this has been primarily in European and U.S. populations. Recent work has shown that not all nasal polyps are highly eosinophilic. Fan *et al.*,²⁴ in a Chinese population with nasal polyp, demonstrated, with an excellent challenge study, that AERD is uncommon (0.57%) in nasal polyps in Chinese subjects, which corresponds with other work that identified a much greater T-helper type 1 or T-helper type 17 bias in nasal polyps in Chinese subjects.^{24–26} It is not unreasonable to conclude that, in ethnic or geographic groups with a noneosinophilic nasal polyp inflammatory pattern, AERD will be much less common.

Current Prevalence Estimation

When taking all of these factors into account, our group concluded that AERD was present in ~7% of adults with asthma and ~9% of patients with nasal polyp.¹¹ In more severe asthma populations, the rate of AERD was as high as 15%.⁵ These numbers can give us a rough approximation of how many patients with AERD are in the United States. Furthermore, these statistics indicate that AERD is more common than many clinicians suspect and might be overlooked. Unlike most other medical conditions, AERD is a discrete disorder within another distinct disorder. Thus, the reason for the anosmia might be correctly identified as nasal polyps, but, if further questioning or evaluation for AERD is not performed, then the AERD diagnosis is missed.

Clinical Predictors

So, what are the factors that can assist the clinician in correctly diagnosing and finding AERD in a larger group of patients with polyp or patients with asthma (Table 1)? Markers of severity should prompt consideration of AERD. These markers would include asthma instability, persistent airflow obstruction, or other factors considered in the TENOR study to be associated with severe asthma.^{4,5} Nasal polyp burden and disease course can also point toward AERD. Early polyp recurrence by 6 months after surgery and the degree of sinus inflammatory changes on computed tomography can both be associated with AERD and raise the suspicion of the diagnosis.³ The degree of inflammation in sinus imaging directly correlates with the finding of a positive oral aspirin challenge result.²⁷ Finally, it has been noted that, in AERD, almost all the patients were intolerant of alcohol, with even small amounts triggering hypersensitive respiratory symptoms.²⁸ Although improvement in alcohol tolerance might occur after aspirin desensitization, that this is not a universal occurrence justifies the conclusion that alcohol does not cause reactions *via* COX-1 inhibition. This phenomenon occurs in patients with asthma who are aspirin tolerant and in patients with non-AERD sinus disease but is far more common in patients with AERD.

A history of an NSAID reaction in the past will assist in making the diagnosis. Certain characteristics of the reactions can be specific for AERD, *viz.*, hospitalization for asthma after NSAID and respiratory reactions to two or more structurally dissimilar NSAIDs.¹⁵ These factors, in combination with a patient with nasal polyposis and asthma, would be strongly predictive of AERD. It is also important to expressly query the patient on any reactions that might occur with NSAID ingestion. Some patients may not consider their nasal congestion to be a “reaction” or an “allergy.” Thus, specific historical clues should be obtained from any patient with asthma or with nasal polyps to assist in determining whether AERD is a diagnostic consideration. Given the prevalence of AERD in up to 15–40% of patients with severe nasal polyposis and asthma (with a negative or questionable history), a diagnosis of AERD can be confirmed after screening only three to eight of such patients with aspirin challenge.

CONCLUSION

All of this is predicated on the importance of making the diagnosis in the first place. Given the success of aspirin therapy in treating respiratory inflammation in AERD, it should be a consideration in any patient with poorly controlled nasal polyps or another reason to be able to take an NSAID or aspirin.^{29–32} Furthermore, given the tremendous advances in our understanding of AERD pathophysiology, it is likely that the endotype specific treatment options in the form of biologics or other more targeted therapies could be uniquely beneficial in AERD. Thus, when the history is unclear, AERD is common enough that diagnostic aspirin challenge should be a strong consideration and be commonly used in the allergist armamentarium.

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