

Aspirin or Other Nonsteroidal Inflammatory Agent Exacerbated Asthma

Dennis K. Ledford, MD^a, Sally E. Wenzel, MD^b, and Richard F. Lockey, MD^c Tampa, Fla; and Pittsburgh, Pa

Aspirin-exacerbated respiratory disease (AERD) is an asthma phenotype with a prevalence that ranges from 2% to 25% of the asthma population. The 2% prevalence applies to patients with mild and 25% to severe, persistent asthma. COX-1–inhibiting nonsteroidal anti-inflammatory drugs, including aspirin, aggravate the preexisting upper and lower respiratory disease, sometimes in a life-threatening manner. The upper airway disease is characterized by an eosinophilic, hyperplastic rhinosinusitis with polyps. Eosinophilia, both peripheral and in the airways with Th2 inflammation, characterizes this disease. The role of allergic sensitivity in AERD is unclear, even though more than 30% of affected patients produce specific IgE to environmental allergens. Clinically, the respiratory symptoms

are not usually associated with allergen exposure. The mechanism responsible for this phenotype is likely related to leukotriene (LT) metabolism because patients who are affected compared with patients who were aspirin tolerant, produce greater amounts of cysteinyl LTs. The synthesis of cysteinyl LTs is further increased after aspirin challenge and symptom exacerbation. Eosinophilia as well as a variety of other biologic markers, for example, Th2 cytokines, peripheral blood eosinophil, and LT enzymes and receptors, are associated with AERD both in the blood and in respiratory mucosa. These markers may help identify patients with AERD, but aspirin or other nonsteroidal anti-inflammatory drugs challenge is the primary means to confirm the diagnosis. A variety of single nucleotide polymorphisms and genes are associated with AERD, but the studies to date are limited to select populations and have not conclusively demonstrated a uniform genetic pattern in subjects with this disease. Treatment of AERD can be challenging because the nasal symptoms, including polyposis, are often refractory to both surgery and medical treatment, and the asthma can be difficult to control. Aspirin desensitization, followed by daily aspirin administration, can improve both upper and lower respiratory tract symptoms in up to 60% of individuals. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2014;2:653-7)

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Aspirin-exacerbated respiratory disease (AERD) is chronic, often severe asthma that is characterized by attacks of bronchoconstriction after the ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID), which inhibit COX-1.^{1,2} AERD is associated with hyperplastic, inflammatory sinusitis, and sinonasal polyps. However, asthma and upper airway disease exist in the absence of any exposure to NSAIDs.³ In 1922, Widal et al⁴ described the association of asthma, nasal polyposis, and aspirin sensitivity, popularized by Samter and Beers⁵ in 1968 and thus also referred to as Samter Triad (asthma, nasal polyps, and aspirin sensitivity). Although it has been assigned many names, AERD best defines this phenotype because this term describes the exacerbation of rhinosinusitis and asthma after the ingestion of aspirin and other COX-1–inhibiting NSAIDs.⁶ The term NERD (NSAID exacerbated respiratory disease) is preferred by some experts to reflect the fact that both aspirin and other NSAIDs exacerbate this chronic disease. AERD will be used in this article.

DEMOGRAPHICS

The actual prevalence of AERD remains uncertain, with reports that range from 2% to 25%.⁷⁻¹⁰ The figures vary,

^aDivision of Allergy and Immunology, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, and the James A. Haley VA Hospital, Tampa, Fla

^bDivision of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh Asthma Institute, University of Pittsburgh, Pittsburgh, Pa

^cDivision of Allergy and Immunology, Morsani College of Medicine, University of South Florida, Tampa, Fla

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Corresponding author: Dennis K. Ledford, MD, Asthma Allergy Immunology Associates of Tampa Bay, 13801 Bruce B Downs Blvd, Suite 502, Tampa, Fla 33613. E-mail: dledford@health.usf.edu.

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Abbreviations used

AERD- Aspirin-exacerbated respiratory disease

ASA- Acetyl salicylic acid (aspirin)

ATA- Aspirin-tolerant asthma

CysLT- Cysteinyl leukotriene

LT- Leukotriene

NERD- Nonsteroidal anti-inflammatory drug exacerbated respiratory disease

NSAID- Nonsteroidal anti-inflammatory drug

PG- Prostaglandin

UTR- Untranslated region

depending on the population surveyed; adults or those with more severe asthma have a higher prevalence of AERD than children or those with mild asthma; the prevalence in adolescence may approach that of adulthood. The evidence to date supports a prevalence of less than 10% in general populations of adults and adolescents with asthma. The apparent prevalence also is increased if the diagnosis is ascertained by self-reporting AERD versus confirmation by aspirin challenge. When examining primarily unblinded, oral provocation tests in a systematic review of 66 articles on AERD, Jenkins et al,⁷ found prevalence rates of 21% and 5% for adults and children, respectively.

AERD may be underdiagnosed, for example, in the European Network of Aspirin-Induced Asthma,¹⁰ 18% of participants were unaware of aspirin sensitivity before undergoing unblinded aspirin provocation tests. The reasons for underdiagnosis may be the lack of recognition of aspirin-exacerbated symptoms by the individual with AERD or low clinical awareness of this syndrome among physicians and other health care professionals. However, caution should be used when evaluating any prevalence studies that used patient reports or unblinded challenges. Zeiss and Lockey¹¹ showed that only 1 of 3 individuals thought to have AERD had positive results when using a double-blinded, controlled challenge protocol.

A variety of aspirin or other NSAID challenge protocols are described in the literature. Most are based on oral ingestion, but nasal, nebulized, and intravenous protocols with compounds, for example, lysine-aspirin also are reported. Lower respiratory symptoms often are mitigated by pretreatment with leukotriene (LT) modifiers; therefore, the specifics of each protocol need to be specified for comparison of prevalence data. Aspirin challenge with unrecognized symptoms and signs, which may occur if challenge is performed while the patient is taking LT modifiers, likely will be misinterpreted as negative challenge. Such false-negative challenges are a potential problem in precise recognition of AERD in both clinical practice and the medical literature.

In 1967, Vanselow¹ first reported an exacerbation of AERD by another NSAID, indomethacin. This was followed by descriptions of symptom exacerbation by other NSAIDs, including ibuprofen, naproxen, and diclofenac. All potent COX-1 inhibitors further exacerbate AERD, whereas COX-2 inhibitors, for example, celecoxib, are tolerated. The age of onset is generally in adulthood, often at ages in the early 30s, with no known racial predisposition. Menstruating female individuals have a greater incidence of AERD than age-matched male individuals.

CLINICAL CHARACTERISTICS

Rhinorrhea and nasal congestion usually are the first symptoms to develop in the course of the disease. The nasal symptoms are perennial and commonly refractory to pharmacotherapy, with

TABLE I. Pathophysiology of AERD: arachidonic acid pathways

Factor	Location
Increased 15 lipoxygenase	Bronchial mucosa
Increased 15 HETE	
Increased 15 LO eoxins	
Increased LTE ₄	Urine, nasal polyps
Increased LTC ₄ synthase	Bronchial mucosa, nasal polyps
Increased cysLTR1 and 2	Bronchial mucosa
Decreased lipoxin A4	Nasal polyps
Decreased PGE ₂	
Decreased E-prostanoid receptor 2	
Decreased COX-2	

HETE, Hydroxyeicosatetraenoic acid; LO, lipoxygenase.

worsening after ingestion of NSAIDs. With time, nasal symptoms become persistent and associated with anosmia, noninfectious recurrent and chronic sinusitis, and nasal polyposis. A patient with AERD develops bronchospasm, which is often severe and life-threatening, within 1 to 3 hours after ingestion of aspirin or other COX-1-inhibiting NSAIDs, usually accompanied by profuse rhinorrhea, conjunctival injection, sometimes a scarlet flushing of the head and neck, periorbital edema, abdominal pain, and minor urticaria. A refractory period to additional aspirin or other COX-1 inhibitors develops after sufficient quantities of one of these medications are given to an individual with AERD. This refractory period lasts for an average of 2 to 4 days.¹¹ AERD compared with aspirin-tolerant asthma (ATA) is more likely to exhibit severe asthma, reduced lung function, increased requirements for systemic glucocorticosteroids, limited control with standard asthma therapy, and a greater risk of life-threatening exacerbations.¹² The asthma and upper airway disease severity may be causally or coincidentally related to the aspirin or NSAID sensitivity.

Aspirin may cause other adverse effects that are distinct from AERD. These include acute urticaria and/or angioedema and exacerbation of chronic urticaria and/or angioedema. Pharmacologic adverse effects include platelet dysfunction associated with bleeding, peptic ulcer disease, and reduced renal blood flow. Reports of anaphylaxis related to aspirin or other NSAID ingestion, with rare exception, are severe AERDs. Specific IgE to aspirin is reported, but its significance is unknown.

COMORBIDITIES

There is evidence of atopic disease in at least one-third of patients with AERD, although the clinical importance of IgE specific to inhaled allergens in its pathogenesis is minimal. However, coexisting allergic respiratory disease may contribute to the disease burden of patients with AERD and should be appropriately treated. Staphylococcal exotoxin-specific IgE, present in the mucus of patients who are affected, along with the exotoxin, may play an important role with upper airway disease and possibly with asthma. Chronic rhinosinusitis can be documented in all, or almost all, affected individuals if sensitive testing, such as computed tomography sinus imaging or nasopharyngoscopy evaluation, is used. Rhinosinusitis tends to progress overtime and is partially responsive to glucocorticosteroid therapy. The severity of the upper airway disease thus will be affected by the duration of symptoms and recent therapy. The upper airway disease may be responsible for the most significant symptoms in some

TABLE II. Pathophysiology of AERD: Th2 and eosinophils

Factor	Location
Increased eosinophilic cationic protein	Nasal polyp
Increased IL-5	Nasal polyp, nasal lavage fluid
Increased RANTES	Nasal polyp
Increased eotaxin	Nasal polyp, peripheral blood
Decreased eosinophil apoptosis	
Increased periostin	Peripheral blood
Increased eosinophils	Nasal polyp, bronchial mucosa, peripheral blood
Increased specific IgE staphylococcal enterotoxin	Nasal polyp
Increased Th2	

TABLE III. Pathophysiology of AERD: inflammation markers

Factor	Location
Increased ApoA1	Peripheral blood
Increased α 2 macroglobulin	Peripheral blood
Increased ceruloplasmin	Peripheral blood

individuals.¹³ Infectious sinusitis, other than chronic staphylococcal infection or colonization, is not a major factor in the pathogenesis of AERD, but acute viral and secondary bacterial infections may aggravate the chronic respiratory disease.

PATHOPHYSIOLOGY

The pathogenesis of AERD is closely linked with dysregulation of LT synthesis. Synthesis of LTs is increased with individuals who are affected and increases further after aspirin challenge. Aspirin affects arachidonic acid metabolism, important in both the prostaglandin (PG) and LT pathways. However, the key mechanism or mechanisms that related LTs and AERD are undetermined. The various factors associated with the pathophysiology of AERD are summarized in [Tables I to III](#).^{14,15} LT production is increased; select PGs and their receptors are decreased; and Th2 cytokines, eosinophils, and eosinophil, and general inflammatory markers are increased. The multiple, potential mechanisms identified either reflect a common pathway that is not yet recognized or multiple disease mechanisms.

GENETICS

The European Network on Aspirin-induced Asthma found that 6% of subjects with AERD had a family history of aspirin hypersensitivity.¹⁰ Case reports of AERD that occur in families, the first one of which was reported in 1972,¹⁶ support the genetic contribution to this disease. However, the low penetrance within families and the lack of a defined pathogenesis makes the search for genetic linkages complicated and confusing. There are relatively small studies in multiple ethnicities, and many of the reports may reflect specific genetic influences limited to a single population (see [Tables E1-E5](#) in this article's Online Repository at www.jaci-inpractice.org).¹⁷⁻²¹

TABLE IV. Suggestive diagnostic criteria for AERD ("NERD")*

History of respiratory symptoms (upper or lower) within 4 h of ingestion of aspirin or other NSAID
Chronic rhinosinusitis†
Nasal polyps†
Peripheral blood eosinophilia (6% or >300/mL)†
Onset of respiratory symptoms >20 y of age

NERD, Nonsteroidal anti-inflammatory drug exacerbated respiratory disease.

*The presence of 4 of 5 criteria without a clinical history of aspirin or other NSAIDs that cause exacerbation of symptoms is sufficient for diagnosis.

†These findings may be influenced by recent therapy with glucocorticoids and the method by which the clinician determines the presence of rhinosinusitis and/or nasal polyps, eg, anterior nasal examination vs nasopharyngoscopy; these criteria are suggestive for clinical decision making and not for confirmation of the diagnosis for research purposes.

BIOMARKERS

There is a 15-fold increase in eosinophils and other cells that expressed LTC₄ synthase in bronchial biopsy specimens of individuals with AERD when compared with subjects without asthma, which is a 4-fold increase when compared with ATA.²² The mechanisms for this increase in eosinophils are not clear, but elevated levels of cysteinyl leukotrienes (cysLT) likely play a role. CysLT levels are increased at baseline in urine and in exhaled air, and rise abruptly after aspirin challenge. CysLT1 receptor antagonists and 5 lipoxygenase inhibitors are both effective in blunting aspirin reactions of individuals who are sensitive, which confirms their therapeutic importance in the acute phase, with some, but not all, experiencing dramatic improvement from chronic therapy as well. Increased cysLT levels correlate with the overexpression of LTC₄ synthase in the bronchial mucosa of AERD.²² Bronchial submucosal mast cells are increased in AERD.^{13,23,24}

Eosinophils and mast cells that express increased 5-lipoxygenase, IL-5, and GM-CSF also were increased in bronchial and nasal biopsy specimens of subjects with AERD.²² With these subjects, increased 5-hydroperoxyicosatetraenoic also was expressed in epithelial cells and increased mast cell mediators, such as PGD₂, tryptase, and histamine, in nasal and sputum secretions. *In vitro* aspirin exposure of isolated blood eosinophils from subjects with AERD versus those with ATA resulted in increased 15-lipoxygenase and 5-lipoxygenase pathway activation and eoxin C₄ production.²⁵ PG metabolism also likely contributes to AERD pathogenesis. Decreased levels of PGE₂ may be a trigger for exacerbation of asthma in AERD because the inhibition of PGE₂ synthesis by COX-1 inhibitors removes PGE₂-mediated restraints on inflammatory cells, and treatment with inhaled PGE₂ blunts these exacerbations.²⁶ Eosinophilia is a characteristic feature of AERD with increased mucosal eosinophils and blood levels. Periostin, a biomarker of Th2 activation and eosinophilic asthma, is associated with AERD versus ATA. Levels of blood periostin correlate with the severity of rhinosinusitis, blood eosinophilia, and sputum eosinophilia in AERD.¹⁵

RELATIONSHIP TO STATISTICALLY DEFINED ASTHMA PHENOTYPES

The heterogeneity of asthma with variable symptom profiles and response to medications necessitate the use of statistical, latent class analyses to identify phenotypes in large cohorts. The analysis generally applied is an unsupervised classification strategy

that uses a hierarchical, bottom-up clustering algorithm method.^{27,28} AERD is associated with more frequent exacerbations and reduced quality of life in a *post hoc* cluster analysis of difficult-to-treat asthma, as defined by the treating physician's subjective assessment and the use of prespecified parameters.²⁷ However, AERD was not defined by challenge in this cohort. AERD has not been specified in other cluster analyses,²⁸⁻³¹ although there are similarities between the AERD associated cluster in 1 study and a more-severe disease cluster in another.^{27,28} Based on available studies, AERD appears to identify a statistically more-severe phenotype.

DEFINITION

In the strictest sense, the AERD phenotype requires confirmation by a blinded aspirin or other NSAID challenge. However, such challenges can be life threatening and expensive, and are unavailable in many clinics. For clinical purposes, a modified definition of AERD may be accepted in patients who fulfill the other 4 specified criteria listed in Table IV. Note that with this definition, a clinical history of aspirin reactions is not absolutely required if all the other criteria are met. The findings of peripheral eosinophilia, rhinosinusitis, and nasal polyps can be modified by recent or concurrent glucocorticoid therapy. A double-blinded challenge, oral, intranasal, or bronchial, is required for a definitive diagnosis in clinical trials or research studies.

RECOMMENDATION FOR INFORMATION TO BE OBTAINED TO DETERMINE AERD PHENOTYPE

1. Does ASA or another NSAID cause wheeze or shortness of breath, chest discomfort, or nasal symptoms?
2. Is there evidence of chronic sinusitis?
3. Is there evidence of nasal polyps with hyposmia?
4. Is there peripheral blood eosinophilia?
5. Did asthma symptoms begin after age 20 years?

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

1. Determine whether prior respiratory infection contributes to the onset of AERD.
2. Determine whether there is a therapeutic value for 5-lipoxygenase inhibitors or other modulators of the LTs or PG pathways compared with LT receptor inhibitors in AERD.
3. Clarify the role of Th2-regulated allergic responses to inhaled allergens in the development of AERD.
4. Clarify the relationship of upper airway inflammation and pathobiology of nasal polyps with lower airway inflammation and asthma in AERD.
5. Determine the important genetic determinants of AERD and relate those to other asthma phenotypes.
6. Verify if the AERD phenotype defined by clinical criteria without ASA and/or NSAID challenge is reliable for epidemiologic, genetic, and mechanistic studies.

CONCLUSION

AERD and its recognition are important clinically to avoid the inadvertent administration of aspirin and other NSAIDs in

the care of these patients. AERD is characterized by severe respiratory disease, both rhinosinusitis and asthma, and is one of the best defined asthma phenotypes, even though the essential pathogenetic mechanisms remain elusive. The association of AERD with altered LT metabolism and increased LT production support the critical role of LTs in its pathogenesis. The complexity of the genetics and the multiple potential mechanisms that link aspirin or other NSAIDs with disease exacerbations have helped and impeded progress in understanding disease pathogenesis. LT synthesis inhibitors and receptor antagonists are helpful for some individuals with AERD but do not provide the degree of control expected based on the increased activity of the LT pathways in AERD. In our opinion and experience, aspirin desensitization and subsequent treatment improve the upper airway disease in approximately 60% of patients, but there is less evidence of asthma benefit. Although genetic associations are confirmed, the adult onset and low genetic penetrance suggest that environmental or infectious factors are important in disease expression. Thus, further research in AERD is needed to better understand the pathogenesis of AERD. If sensitive and specific biomarkers or genetic markers can be determined, perhaps at-risk cohorts could be identified and followed to better understand the onset and pathogenesis of AERD.

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TABLE E1. Single nucleotide polymorphism markers of AERD associated with LT metabolism

Gene	Region of gene	Population studied
CysLT receptor 1	Promotor	Korean
	Exon	British, Spanish, Tristan da Cumba
CysLT receptor 2	Promotor	Japanese
	Exon	White
	3'UTR*	Korean
LTC4 synthase	Promotor	Japanese, Korean, Polish, US
ALOX 5	Promotor	Japanese, US
	Ht1	Korean

UTR, Untranslated region.

*Untranslated region repeat at the 3' end of the gene.

TABLE E2. Single nucleotide polymorphism markers of AERD associated with PG metabolism

Gene	Region of gene	Population studied
PGE receptor 2	5' Upstream*	Japanese
	Promotor	Korean
PGE receptor 3	Promotor	Korean
	Intron	Korean
	3'UTR†	Korean
PGE receptor 4	Promotor	Korean
PGI2	3'UTR†	Korean
Thromboxane A1 synthase	Intron	Korean
Thromboxane A2 receptor	Promotor	Korean
	Exon	Korean
Regulator of G protein signaling 7-binding protein		Korean

UTR, Untranslated region.

*Upstream from the 5' starting point of the gene.

†Untranslated region at the 3' end of the gene.

TABLE E3. Single nucleotide polymorphism markers of AERD associated with immunologic response

Gene	Region of gene	Population studied
HLA-DQ		White
HLA-DPB1	Exon	British, German, Polish
IL-4	Promotor	Korean
IL-13	Promotor	Korean
T Box expressed in T cells	Promotor	Japanese
FCER1A	Promotor	Korean
FCER1B	Promotor	Korean
FCER1G	Promotor	Korean
Toll-like receptor 3	5'UTR*	Korean
	Exon	Korean
Nod-like receptor family pyrin domain containing 3	Intron	Japanese
Activating transcription factor 6β	Promotor	Korean
	Exon	Korean
	3'UTR†	Korean
Transporter associated with antigen processing-binding protein	Exon	Korean
	3'UTR†	Korean

UTR, Untranslated region.

*Untranslated region repeat at the 5' end of the gene.

†Untranslated region repeat at the 3' end of the gene.

TABLE E4. Single nucleotide polymorphism markers of AERD associated with tissue remodeling

Gene	Region of gene	Population studied
A Disintegrin and Metalloproteinase Domain 33	Intron	Japanese
	Exon	Japanese
Fibrous Sheath Interacting Protein 1	Intron	Korean
Emilin/Multimerin Domain Containing Protein 2	Intron	Korean
Angiotensin 1 Converting Enzyme	Promotor	Korean
Adenosine A1 Receptor	3'UTR*	Korean
	Exon	Korean
Adenosine A2a Receptor		
G Protein Coupled Receptor 44	Promotor	Korean
Peroxisome Proliferation-Activated Receptor Gamma	Promotor	Korean
Kinesin Receptor Family Member 3A	Intron	Korean
Sparc-related Modular Calcium-Binding Protein 2	Intron	Korean

*Untranslated region repeat at the 3' end of the gene.

TABLE E5. Single nucleotide polymorphism markers of AERD associated with neural physiology

Gene	Region of gene	Population studied
Solute Family 6 (Neurotransmitter Transporter betaine/gaba) Member 12	Intron	Korean
Solute Carrier Family Y22	Exon	Korean
Calcium Channel Voltage Dependent Gamma 6 Subunit	Intron	Korean
Annexin A4	Promotor	Korean
	Intron	Korean
	Exon	Korean

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