

Diagnostic Evaluation in Aspirin-Exacerbated Respiratory Disease



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KEYWORDS

- Aspirin-exacerbated respiratory disease • Diagnosis • NSAID hypersensitivity
- Chronic rhinosinusitis with nasal polyps • Asthma • Intranasal ketorolac
- Oral aspirin challenge • Lysine-aspirin

KEY POINTS

- The diagnosis of aspirin-exacerbated respiratory disease (AERD) is based on the history and confirmed by nonsteroidal anti-inflammatory drug (NSAID) provocation challenge.
- Options for diagnostic challenge include lysine-aspirin challenge by intranasal or inhalation (not available in the United States), oral aspirin challenge, and intranasal ketorolac and modified oral aspirin challenge.
- Oral aspirin challenge is considered the gold standard for diagnosis of AERD.
- Positive provocation challenges result in respiratory and systemic reactions of varying degrees of severity requiring close monitoring and treatment.
- Positive provocation challenges are usually performed as the initial step to NSAID desensitization.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is widely accepted as a distinct clinical disease, characterized classically by the triad of chronic hyperplastic, eosinophil-rich rhinosinusitis with nasal polyps; asthma; and hypersensitivity reactions to inhibitors of cyclo-oxygenase 1 enzyme (COX-1), such as nonsteroidal anti-inflammatory drugs (NSAIDs). Distinguishing the clinical triad of AERD from other phenotypes of chronic rhinosinusitis with nasal polyps (CRSNP), asthma, and NSAID reactivity is very important for 2 main reasons.

First, patients with AERD are at risk of experiencing very distressing and even life-threatening reactions following ingestion of NSAIDs. In cases of uncertainty regarding

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tolerance of NSAIDs, patients with AERD would need to be counseled that future ingestion of NSAIDs could result in serious reactions, whereas individuals with CRSNP and/or asthma who do not have AERD should not be unduly restricted from taking these NSAIDs when clinically indicated for anti-inflammatory, analgesic, or cardiovascular benefit.

Second, there are treatment modalities uniquely beneficial in patients with AERD as compared with other phenotypes of CRSNP and asthma. As noted elsewhere in this journal, treatment with antileukotriene therapy and long-term treatment with aspirin following aspirin desensitization can have significant therapeutic benefit in AERD.

Although establishing the diagnosis of AERD is important for a number of reasons, making an accurate diagnosis can be challenging. This article is intended to assist the clinician in using the medical history and clinically available diagnostic modalities to accurately identify those patients with AERD, so that they may benefit from the therapies useful in this condition.

DIAGNOSTIC UTILITY OF THE CLINICAL PRESENTATION

The diagnosis of AERD is suggested based on the clinical presentation and confirmed when an individual with a history suggestive of AERD has a clinically observed reaction to aspirin or another NSAID administered by 1 of 3 routes: intranasal, inhalation, or oral ingestion (oral aspirin challenge [OAC]).

Awareness of the prevalence of AERD in patients with CRSNP and asthma can be helpful in the approach to diagnosing AERD. Estimates of the prevalence of AERD in individuals with asthma, CRSNP, or both vary widely depending on the disease severity and means of diagnosis. A recent meta-analysis of several epidemiologic studies found the prevalence of AERD in certain populations to be

- 7% asthma
- 15% severe asthma
- 10% nasal polyps
- 9% unspecified chronic rhinosinusitis¹

Although the history is helpful in making the diagnosis of AERD, it should not be relied on exclusively. Many patients with AERD may not be aware of their NSAID hypersensitivity. The onset of the reaction can be delayed by 2 to 3 hours after NSAID ingestion, making it difficult for the patient to make the connection between NSAID ingestion and any sudden increase in respiratory symptoms. Some patients with CRSNP and asthma may not have an occasion to take NSAIDs after the onset of disease, whereas others may have been advised to avoid NSAIDs before NSAID intolerance is suggested or confirmed. A European study reported that 15% of patients confirmed to have AERD after a positive challenge were not aware of their NSAID hypersensitivity before challenge.²

Dursun and colleagues³ examined the value of the history provided by the patient in the diagnosis of AERD. In this study involving 243 patients with asthma and CRSNP referred for OAC, prechallenge data were collected from patient recall and available medical records regarding the details of the clinical history, including number and severity of NSAID-induced reactions before presentation. Of the 12 patients who had always avoided NSAIDs, and therefore did not know if they could tolerate taking NSAIDs, 5 (42%) had a positive challenge. The chance of a positive OAC if the patient had at least 1 suspected NSAID reaction was 86%. Patients with 2 or more prior NSAID-induced reactions had an 89% chance of having a positive OAC. In patients with at least 1 severe reaction (defined as a poor response to albuterol and requiring

medical intervention), 100% had a positive OAC result. In a multivariate analysis of several characteristics, the following were associated with a statistically significant higher likelihood of having a positive OAC:

- Multiple NSAID-induced reactions
- Age ≤ 40 years
- Poorer sense of smell³

DIAGNOSTIC NONSTEROIDAL ANTI-INFLAMMATORY DRUG CHALLENGE

The diagnosis of AERD is confirmed with objectively observed signs of a hypersensitivity reaction provoked by graded inhalation, intranasal, or oral administration of NSAIDs. In Europe and other parts of the world, inhalation and intranasal provocation challenge testing has been widely available because of the availability of lysine-aspirin, a form of aspirin that is soluble and can therefore be administered in respirable droplets. In the United States, lysine-aspirin is not approved for use in humans by the US Food and Drug Administration. As a result, the only means of diagnostic provocation that had been available in the United States was provocation by oral challenge. In recent years, however, ketorolac tromethamine, an NSAID available in aqueous solution, has been used in intranasal challenge and is gaining wider acceptance and increasingly used in the diagnosis of AERD.^{4,5}

OAC is considered the gold standard for confirming the diagnosis of AERD, with the greatest sensitivity.⁶ **Table 1** lists the sensitivity and specificities of currently available provocation modalities. There are a number of variations of protocols for each type of diagnostic challenge technique that have been published and/or are in clinical use, limiting reliable comparisons in test performance.

Indications and Contraindications for Diagnostic Challenge

The importance of diagnosing, or ruling out, AERD in patients with CRSNP and asthma cannot be overemphasized, as the implications for management are significant. Diagnostic NSAID challenge in patients with CRSNP and/or asthma is indicated in 2 main situations. First, it is used to determine NSAID tolerance status when it is not known. Many patients with CRSNP and/or asthma do not know whether they are able to tolerate NSAIDs, either because they are intentionally avoiding NSAIDs out of caution, have not had occasion to take NSAIDs, or have never temporally associated triggering of respiratory symptoms with taking NSAIDs.

Second, NSAID challenge is indicated to confirm the diagnosis of AERD in patients with CRSNP, asthma, and strongly suspected NSAID intolerance who have an indication for therapeutic use of NSAIDs, such as in the management of AERD, for cardiovascular benefit, or for anti-inflammatory or analgesic effects.

Table 1
Sensitivity and specificity of diagnostic challenges for aspirin-exacerbated respiratory disease

Route of Challenge	Sensitivity, %	Specificity, %
Oral	89–90	93
Bronchial	77–90	93
Intranasal		
Lysine-aspirin	80–87	93–100
Ketorolac	56–90	64–94

Data from Refs.^{4,5,7–12}

Contraindications for Diagnostic Challenge

NSAID challenges are considered contraindicated in patients with any of the following:

- History of severe anaphylactic reactions precipitated by aspirin or NSAIDs
- Unstable asthma
- Recent respiratory tract infection (within 4 weeks)
- Current pregnancy
- Severe underlying cardiovascular, renal, or liver disease¹³

Patients receiving therapy with beta-blockers may be at increased risk of more severe and difficult-to-treat reactions. Some guidelines consider beta-blockers to be a contraindication, whereas others recommend taking additional precautions in patients who are unable to stop taking them.^{13,14}

Preparation for Diagnostic Challenge

NSAID challenges should be conducted under the supervision of a physician with experience in recognizing and treating severe respiratory or systemic reactions and in centers with the necessary equipment for emergency resuscitation. Patients should be in stable condition and most guidelines recommend baseline forced expiratory volume in 1 second (FEV1) should be at least 60% to 70% predicted value. In patients with more compromised lung function who are undergoing inhalation challenge or OAC, initiation or escalation of oral corticosteroids should be considered. Intravenous line placement is recommended. Full informed consent should be obtained in all cases.^{13,14}

Where lysine-aspirin is available, intranasal lysine-aspirin challenge can be performed in the outpatient setting.¹³ In the case of OAC, accumulating experience and evidence supports performing OACs in the outpatient setting as long as the following criteria are met:

- Stable lung function and FEV1 $\geq$ 60% predicted
- Premedication with antileukotriene therapy and other appropriate asthma controller therapy
- Physician and nursing personnel experienced in OACs are present, and close monitoring is feasible¹⁵

Performing diagnostic challenges when the outcome is uncertain presents a potential challenge in clinical decision-making with regard to management of respiratory medications leading up to the challenge. The risks of withdrawing medications used for the treatment of asthma and/or CRSNP in hopes of not masking the signs and symptoms used to determine a positive test should be weighed against the benefits of continuing medications that may mask a positive result but create a safer outcome. Few studies have examined which medications have the potential to mask a positive reaction leading to a false-negative challenge. A study by White and colleagues¹⁶ suggested that antileukotriene therapy, oral corticosteroids, inhaled corticosteroids, and long-acting beta-agonists appeared to reduce the risk of lower airway reactions in the oral challenge setting, but did not mask respiratory reactions. Other studies have suggested that antihistamines, leukotriene receptor antagonists, and 5-lipoxygenase inhibitors have the potential to mask a positive challenge.^{17–21} However, because of studies that support enhanced safety of OACs in patients taking antileukotriene therapy and other controller therapy, current practice in the United States is to initiate or continue antileukotriene therapy, inhaled corticosteroids, and long-acting beta-agonists in preparation for OACs.^{14–16,22} European guidelines, on the other hand,

recommend conducting OACs after withdrawing antileukotriene therapy and long-acting beta-agonists.¹³ **Table 2** lists the recommendations for medication withdrawal before NSAID challenges.

Treatment of Positive Nonsteroidal Anti-Inflammatory Drug Challenges

Patients undergoing aspirin challenge should be warned that an NSAID-induced reaction is likely to occur that may require inhaled beta-agonists and even intramuscular epinephrine. Once a positive challenge has occurred, optimizing patient safety necessitates early, aggressive, and appropriate treatment of the reaction. **Table 3** lists treatment options for the most commonly observed reactions provoked by NSAID challenge. Anaphylaxis should be treated as outlined in anaphylaxis treatment guidelines.^{23,24}

Inhalation/Bronchial Challenge

First introduced in 1977, inhalation lysine-aspirin challenge is considered to be safer and less time-consuming than oral challenge but not as sensitive.^{13,25} Systemic reactions to bronchial challenge have been reported.²⁶ In a protocol published in European guidelines, lysine-aspirin is administered as a graded challenge by nebulization beginning with a dose of 0.18 mg lysine-aspirin. Incrementally increasing doses are administered every 30 minutes, with FEV1 monitoring at baseline and every 10 minutes to a maximum cumulative dose of 181.98 mg.¹³ The challenge is considered to be positive if FEV1 decreases by $\geq 20\%$ as compared with baseline FEV1. The provoking dose (PD20) is then calculated and recorded. The challenge takes approximately 4 hours to complete. Because of the reduced sensitivity of inhalation challenge as compared with oral challenge, oral challenge is recommended following a negative inhalation challenge.¹³

Intranasal Challenge

Intranasal challenge with lysine-aspirin or ketorolac has the advantage of being less likely to provoke a severe systemic or lower respiratory response, and is therefore

Table 2
Medication withdrawal before diagnostic nonsteroidal anti-inflammatory drug challenge

Medication	European Guidelines		US Guidelines
	Nasal	Bronchial/Oral	
Oral antihistamines	24 h	3 d	48 h
Oral decongestants	24 h	—	48 h
Nasal cromolyn	24 h	—	—
Leukotriene modifiers	≥ 7 d	≥ 7 d	—
Oral corticosteroids	7 d	—	—
Nasal corticosteroids	7 d	—	—
Inhaled corticosteroids	—	—	—
Long-acting beta-agonists	—	24–48 h	—
Short-acting beta-agonists	—	6–8 h	6–8 h
Inhaled anticholinergics	—	24 h	—

Data from Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–8; and Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. *Ann Allergy Asthma Immunol* 2007;98:172–4.

Table 3 Treatment of positive NSAID challenges	
Organ System	Medication Options
Ocular	Oral antihistamines, ocular antihistamine/mast cell stabilizers
Nasal	Oral or nasal antihistamines, oral or nasal decongestants
Bronchial	Inhaled beta-agonists, inhaled anticholinergics
Laryngeal	Inhaled racemic epinephrine, intramuscular epinephrine
Cutaneous	Oral or intravenous antihistamines
Gastrointestinal	Oral or intravenous H ₂ -antihistamines, anti-dopaminergic anti-emetics
Vascular (hypotension)	Intramuscular epinephrine

Adapted from Joint Task Force on Practice Parameters. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:273.e41.

considered safer.^{5,13} It should be noted, however, that systemic and lower airway reactions have been reported with intranasal ketorolac.⁵ Intranasal lysine-aspirin challenge may be particularly useful in patients who lack clinically apparent asthma, who have severe or unstable lower airway disease, or who are at high risk of severe systemic or lower airway reactions.¹³ Disadvantages include limitations of use in patients with severe nasal obstruction by massive, anteriorly extending polyps and reduced sensitivity. Four methods of assessment of response to nasal challenge include symptoms, acoustic rhinometry, active anterior rhinomanometry, and peak nasal inspiratory flow (PNIF).¹³

Intranasal Lysine-Aspirin Challenge

After baseline assessment of symptoms and objective measurement of nasal patency and/or flow, intranasal saline is administered to evaluate for nonspecific nasal hyper-reactivity. If there is a 20% change from baseline measurements after saline administration, the specificity of any attempt to provoke symptoms with lysine-aspirin would be very low and the challenge should not proceed further. Once nonspecific hyper-reactivity is excluded, lysine-aspirin 80 µL (total aspirin dose of 16 mg) is instilled into each nostril and the patient’s head is tilted back for 1 minute. Symptom and objective assessments are made every 10 minutes for 2 hours.

A positive response is defined as the development of nasal symptoms such as rhinorrhea, nasal congestion, or sneezing and a reduction in objective measurements of nasal patency and/or flow. For acoustic rhinometry, a positive test is defined as a ≥25% decrease from baseline in total nasal flow value at 12 cm. In the case of rhinomanometry or PNIF, a 40% decrease in flow as compared with baseline is required for a positive test. A study comparing the test performance characteristics of acoustic rhinometry and PNIF found acoustic rhinometry to have better sensitivity.²⁷ Because of the reduced sensitivity of intranasal challenge, a negative nasal challenge should be followed by OAC.¹³

Intranasal Ketorolac and Modified Oral Aspirin Challenge

The barrier to topical airway provocation challenge in AERD presented by the lack of access to an aqueous NSAID (such as lysine-aspirin) in the United States was overcome by the development of intranasal ketorolac challenge by White and colleagues⁴ in 2006. In this approach, ketorolac is applied to the nasal passage by metered dose nasal spray bottle, using incremental doses administered every 30 minutes with PNIF and spirometry measured before each dose (Table 4). A positive challenge is

Table 4
Intranasal ketorolac and modified oral aspirin challenge dosing protocol

Day	Interval, min	Ketorolac			Aspirin	
		Sprays, no.	Dose, mg	Cumulative Dose, mg	Dose, mg	Cumulative Dose, mg
1	—	1 in 1 nostril	1.26	1.26	—	—
	30	1 in each nostril	2.52	3.78	—	—
	30	2 in each nostril	5.04	8.82	—	—
	30	3 in each nostril	7.56	16.38	—	—
	60	—	—	—	60	60
	60	—	—	—	60	120
	90	(Observation)	—	—	—	—
2	—	—	—	—	150	270
	180	—	—	—	325	595
	180	(Observation)	—	—	—	—

Data from Lee RU, White AA, Ding D, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2010;105:130–5.

defined as development of symptoms of rhinitis, conjunctivitis, or bronchospasm with a decrease in PNIF of $\geq 20\%$ and/or a decrease in FEV1 by $\geq 15\%$ from baseline.^{4,5} The dose provoking a positive reaction is repeated before progressing to the next dose.

The initial study of the use of intranasal ketorolac alone reported a sensitivity of 78% and a specificity of 64% for the diagnosis of AERD.⁴ As a result, if the maximum dose of 3 sprays per nostril (total cumulative dose of ketorolac 16.38 mg) is reached without symptoms, a modified oral challenge is then performed. Preliminary results indicate that this is a safe technique, with a reduced risk of laryngospasm and gastrointestinal side effects. The intranasal ketorolac and modified OAC take an average of 1.9 days to complete.⁵

Oral Aspirin Challenge

Oral aspirin challenge is considered to be the most conclusive way to confirm the diagnosis of AERD.^{6,28} A number of protocols have been published for the purpose of OAC, and in most cases, these protocols are designed to convert a positive challenge into a completed desensitization in a single procedure. Four variations of published OAC protocols are presented in [Table 5](#).

Baseline symptoms, FEV1, vital signs, and objective measurement of nasal flow/patency (where available) are assessed at baseline and at 30-minute to 60-minute intervals. Incremental doses are then given as dictated by the protocol until signs or symptoms of a reaction are observed. A positive oral challenge is defined by 1 or more of the following:

- Obvious signs and symptoms of respiratory reaction
 - Upper respiratory reaction (rhinorrhea, nasal congestion, sneezing, increased lacrimation)
 - Bronchospasm (coughing, wheezing, chest tightness, dyspnea)
 - Laryngospasm (stridor, dysphonia)
- Decrease in FEV1 by $\geq 15\%$ or $\geq 20\%$ (depending on the center)
- Decrease in nasal flow and/or patency (see section on Intranasal Lysine-Aspirin Challenge)

Table 5 Examples of published oral aspirin challenge protocols			
Protocol Source	Dosing Interval, min	Doses, mg	Time to Complete, d
Scripps Clinic ¹⁵	180	20–40, 40–60, 60–100, 100–160, 160–325, 325	≥2
EAACI Guidelines ¹³	90–120	10 ^a , 27, 44, 117, 312, 500	≥1
Aspirin Desensitization Joint Task Force ¹⁴	90	20.25, 40.5, 81, 162.5, 325	≥1
UTSW Medical Center ²⁹	60	20 ^a , 40, 81, 120, 162, 325	≥1

Abbreviations: EAACI, European Academy of Allergy and Clinical Immunology; UTSW, University of Texas Southwestern.

^a Lower starting dose is used if the patient has a history of a severe nonsteroidal anti-inflammatory drug–induced reaction.

Once AERD is confirmed with a positive reaction, the symptoms are treated aggressively (see [Table 3](#)). Once the symptoms have been controlled, most centers proceed with the process that leads to desensitization. This entails repeat administration of the provoking dose until no reaction is observed, then continuing with incremental doses as dictated by the protocol, repeating any dose that elicits further airway reactions before proceeding to the next dose.^{13–15,28–30}

Starting doses and dosing intervals vary widely between published OAC protocols. The cited reason for this variation has to do with balancing time efficiency of the procedure with the risk of administering escalating doses prematurely. When a 3-hour dosing interval is used, the mean time elapsed from ingestion of the provoking dose of aspirin to onset of reaction was found to be 102 minutes and the mean provoking dose to be 68 mg, with most positive challenges occurring after doses of 45 to 100 mg aspirin.³¹ Using a 60-minute dosing interval, Chen and colleagues²⁹ found the mean time to onset of symptoms to be 50 minutes and the mean provoking dose to be 157 mg. Whether the apparent shorter time to onset of symptoms and higher provoking dose in the latter study are due to attributing provocation of the reaction to the incorrect dose is not known. A theoretic concern of using a dosing interval of less than 90 minutes is that not enough observation time elapses to permit identification and treatment of a reaction in many patients before the next dose is given. Whether protocols with shorter dosing intervals are associated with more severe or difficult-to-treat OAC reactions has not been extensively evaluated. The preliminary report of 57 patients who underwent OAC and desensitization with the 60-minute dosing-interval protocol suggests this to be a safe approach in select patients.²⁹

Most (90%–98%) positive oral challenges include a naso-ocular reaction, and 35% to 90% include a bronchial reaction.^{29,31–33} Positive reactions also can include gastrointestinal symptoms (eg, abdominal pain, nausea, vomiting), cutaneous symptoms (eg, hives, itching, flushing), and laryngeal symptoms (eg, laryngeal edema or laryngospasm) with a frequency of 23%, 10%, and 8%, respectively, according to one analysis.³² Hypotension also has been reported.¹⁶

Hope and colleagues³¹ sought to identify risk factors that might predict a more severe bronchial reaction. Multivariate analysis suggested that the clinical predictors of moderate-to-severe bronchial reactions (defined as >20% decrease in FEV1 from pre-challenge baseline) include the following:

- Lack of prechallenge treatment with anti-leukotriene therapy
- Duration of symptoms of AERD ≤ 10 years

- Baseline FEV1 less than 80% predicted
- Prior emergency room visit for asthma exacerbation other than caused by NSAIDs, and lack of leukotriene modifier therapy at the time of challenge³¹

If 3 or more risk factors were present, the risk of a moderate-to-severe reaction was 43%.³¹ On the other hand, the severity of the reaction reported by patients before OAC does not predict the severity of the reaction observed during OAC, with observed challenge reactions generally being milder.³²

A negative challenge is defined as completing the challenge protocol until the maximum dose is reached (usually 325 mg aspirin) without any of the signs, symptoms, or objective measures of airway reaction defined previously. A patient with a high prechallenge probability of AERD, based on the available history, who then has a negative challenge presents a special challenge. The reported sensitivity of OAC of 90% indicates that the possibility of a false-negative challenge exists.^{7,8,21} In addition, White and colleagues²¹ reported a case series illustrating the clinical dilemma of “silent desensitization” in which patients with initial negative OACs were later confirmed to have AERD on repeat challenge. An approach to the patient with a high suspicion for AERD but a negative OAC involves either (1) repeat challenge when the patient is not receiving leukotriene therapy and oral steroids, perhaps including higher aspirin challenge doses, or (2) presumptive diagnosis of AERD and continuation of therapeutic doses of aspirin with assessment of symptom response at 6 months.²¹

In Vitro Diagnostic Testing

Currently, the only reliable means of confirming the diagnosis of AERD is by provocation of respiratory or systemic hypersensitivity NSAID reactions. In vitro testing for AERD would offer a safer alternative to the current approach. A number of approaches are in development but none have proven to be reliable enough for clinical practice at this time. Examples include the cellular activation stimulation test, leukotriene release assay, basophil activation test, and the 15-hydroxyeicosatetranic acid assay (ASPISTest).^{34–41}

SUMMARY

In most cases, patients with clinical features of AERD would benefit from evaluation by a respiratory specialist with expertise in the diagnosis and management of AERD. Confirmation or exclusion of the diagnosis of AERD has important clinical implications. Most patients present with CRSNP, asthma, and a history of one or more episodes of respiratory or systemic reactions to ingestion of NSAIDs, whereas a smaller number of patients with CRSNP and/or asthma are uncertain as to their ability to tolerate NSAIDs. In the first case, diagnostic NSAID challenge is typically performed as part of aspirin desensitization, which confirms the diagnosis and permits long-term therapeutic use of aspirin. In the second case, NSAID challenge should be performed to either free the patient without AERD from the burden of lifelong NSAID avoidance or to confirm the presence of AERD and the management implications that this entails.

In experienced hands, these diagnostic challenges are relatively safe and increasingly performed in the outpatient setting. Where available, lysine-aspirin inhalational or intranasal challenges have an excellent safety record. OAC remains the gold standard for confirming the diagnosis of AERD. In the United States, the use of antileukotriene premedication and the development of intranasal ketorolac and modified OAC have contributed to enhanced safety of diagnostic challenges, as well.

Future work in the diagnosis of AERD will likely focus on continued efforts to optimize the safety and time efficiency of performing these diagnostic challenges in the outpatient setting. The hope of an accurate in vitro diagnostic test for AERD also remains.

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