



Current approach to the diagnostic value of aspirin provocation tests in nonsteroidal anti-inflammatory drug exacerbated respiratory disease: indications, methodology, safety, and clinical applications

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Abstract

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is a respiratory illness characterized by chronic eosinophilic airway inflammation. Although a typical clinical history of asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and respiratory reactions to NSAIDs may strongly suggest the diagnosis, history alone is often unreliable due to NSAID avoidance, atypical reactions, or incomplete symptom recognition. In this context, aspirin provocation tests remain the diagnostic gold standard for confirming N-ERD. Beyond diagnostic confirmation, aspirin provocation testing provides critical insights into disease heterogeneity and phenotyping. Different challenge routes—nasal, bronchial, and oral—allow assessment of organ-specific sensitivity and inflammatory dominance. Nasal aspirin provocation primarily reflects upper airway involvement and is particularly informative in patients with severe CRSwNP, whereas inhalational lysine-aspirin challenges highlight lower-airway bronchial hyperresponsiveness. Oral aspirin provocation, through systemic exposure, captures the full spectrum of respiratory and extra-respiratory responses and therefore best reflects global disease severity. The pattern, timing, and intensity of reactions observed during provocation testing contribute to the identification of clinically relevant N-ERD subphenotypes, such as upper-airway-dominant disease, bronchial-predominant disease, or blended reactions involving both compartments. These phenotypic distinctions have direct therapeutic implications, influencing the selection of targeted treatments, including aspirin desensitization, biologic therapies, or surgical interventions. Moreover, provocation testing remains essential prior to aspirin desensitization to ensure both diagnostic accuracy and patient safety. Aspirin provocation tests are not merely confirmatory tools but represent a cornerstone of precision-based evaluation of N-ERD, enabling refined phenotyping, risk stratification, and individualized treatment planning in this complex and heterogeneous disease.

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Keywords

asthma, non-steroidal anti-inflammatory drugs, allergy, nonsteroid exacerbated respiratory disease, aspirin provocation tests, diagnosis, phenotypes

Introduction

Non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) is a respiratory illness characterized by chronic eosinophilic airway inflammation. Initially referred to as aspirin-induced asthma, aspirin-exacerbated respiratory disease, or Samter's triad, this clinical entity has recently been unanimously agreed upon as N-ERD [1, 2]. This clinical triad typically includes hypersensitivity to aspirin and other NSAIDs, asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP). The prevalence of N-ERD in the general population ranges from 0.3% to 1.9% [3–5]. The prevalence rises to 7–9% in patients with asthma and to 15% in patients with severe asthma [2, 6]. Among patients with CRSwNP, the prevalence ranges from 9–15% [6].

In the updated classification of hypersensitivity reactions to NSAIDs, the cross-intolerant group is led by N-ERD, characterized by asthma and CRSwNP, and symptoms such as bronchospasm, wheezing, rhinitis, or rhinorrhea following NSAID exposure. NSAID-exacerbated cutaneous disease (NECD), a cutaneous disorder with exacerbation following NSAID use on a background of chronic urticaria/angioedema, is characterized by urticaria and/or angioedema after multiple NSAIDs. NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA) occurs in otherwise healthy individuals without chronic urticaria [7].

Several key investigations have demonstrated that the pathophysiology of N-ERD stems from an imbalance in arachidonic acid metabolism, in which cyclooxygenase-1 (COX-1) inhibition leads to diminished prostaglandin E2 production and an overexpression of cysteinyl leukotrienes [8]. Early clinical studies provided biochemical confirmation by showing significant elevations in urinary leukotriene E4 following aspirin challenge, underscoring the pivotal role of leukotriene pathways [9]. Later mechanistic research highlighted increased prostaglandin D2 release, enhanced mast cell activation, platelet-leukocyte crosstalk, and sustained eosinophilic inflammation within the airways as major contributors to disease expression [10, 11]. Complementary molecular analyses of nasal polyp tissue revealed aberrant COX-2 expression and broader lipid mediator dysregulation, reinforcing the current understanding of N-ERD as a chronic type-2 inflammatory condition driven by disrupted lipid signaling networks [12].

In N-ERD, dyspnea is the most prominent clinical symptom observed in most patients after NSAID intake. A decrease in forced expiratory volume in one second (FEV1) of more than 20% and laryngospasm may also occur. On the other hand, nasal symptoms constitute another major symptom. Eye symptoms may also be present [13–15]. Clinical symptoms typically begin 30–180 minutes after drug ingestion. Twenty percent of patients may develop urticaria (hives) or generalized skin redness, and eight percent may develop noticeable swelling, particularly in the face [10, 13].

Before NSAID sensitivity develops, the N-ERD clinical picture gradually begins with rhinorrhea and nasal congestion, progressing to anosmia and CRSwNP. Asthma usually develops after approximately 2 years. NSAID sensitivity is observed approximately 5 years after the onset of nasal symptoms [13].

Recent studies have confirmed the heterogeneity of the clinical presentation of N-ERD. Most studies (cluster analyses from Korea, Japan, Europe, and the U.S.) consistently identify 3–4 primary sub-phenotypes [2, 16–18] (Table 1). In these clinical sub-phenotypes, in addition to the classical presentation of N-ERD, upper airway dominant or lower airway dominant phenotypes can be seen. The primary importance of determining these clinical subphenotypes lies in providing the most appropriate individualized therapeutic option for patients with N-ERD (Table 1).

Table 1. Subphenotypes of N-ERD.

| Subphenotype | Main features | Polyps | Inflammation | Test reaction | Best treatments |
|--|-------------------------------|---------------|----------------------|--------------------|---------------------------------------|
| Classic N-ERD (severe eos) | Severe asthma + recurrent CRS | Very severe | High T2/eos | Strong, low-dose | Biologics, LTRAs, surgery |
| Moderate N-ERD (upper-airway dominant) | CRS > asthma | Moderate | Medium T2 | Nasal-dominant | ATAD, corticosteroids |
| Non-T2/neutrophilic | Less nasal polyp, atypical | Mild/None | Low T2, neutrophilic | Mild | Macrolides, stepwise asthma treatment |
| Atopic N-ERD | Allergy-driven asthma | Mild/Moderate | High IgE | Moderate | Anti-IgE |
| Lower-airway dominant | Severe asthma > CRS | Mild | Mixed | Bronchial-dominant | Biologics |

N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease; CRS: chronic rhinosinusitis; T2: type 2 inflammation; eos: eosinophilic; IgE: immunoglobulin E; LTRAs: leukotriene receptor antagonists; ATAD: aspirin treatment after desensitization.

Overview of aspirin provocation testing

Aspirin provocation testing plays a central role in the diagnosis and phenotypic characterization of N-ERD [19–21]. Although a typical clinical history of asthma, CRSwNP, and respiratory reactions to NSAIDs may strongly suggest the diagnosis, history alone is often unreliable due to NSAID avoidance, atypical reactions, or incomplete symptom recognition. In this context, aspirin provocation tests remain the diagnostic gold standard for confirming N-ERD [1, 19, 20]. This test is designed to assess a patient’s hypersensitivity in a controlled environment by administering increasing doses of aspirin.

Beyond diagnostic confirmation, aspirin provocation testing provides critical insights into disease heterogeneity and phenotyping. Different challenge routes—nasal, bronchial, and oral—allow assessment of organ-specific sensitivity and inflammatory dominance.

Types of aspirin provocation tests

There are four types of aspirin provocation tests: Oral, bronchial, nasal, and intravenous provocations.

Oral aspirin provocation test (OAPT)

The oral provocation test with aspirin is generally considered the gold standard because it best mimics natural exposure [1]. It is particularly reliable and is more frequently preferred in demonstrating systemic reactions, with a sensitivity of 89% and a specificity of 93% [20].

The indications for OAPTs are:

1. To confirm or rule out the diagnosis of NSAID/aspirin hypersensitivity when there is a history of a single episode, a very old reaction, a story with forgotten details, other accompanying triggers, etc.
2. Determining the provocation threshold dose before desensitization.
3. If inhalation or nasal aspirin/lysine-aspirin provocations are negative but clinical suspicion persists, an oral aspirin challenge is indicated to clarify the diagnosis [19].

Oral provocation tests should be performed in a clinical setting with experienced physicians and healthcare personnel. A period should be chosen before initiating the procedure when the patient is clinically stable, and their FEV1 value is above 70% [1, 19, 20]. Short-acting B2 agonists should be discontinued 8 hours before, long-acting B2 agonists and tiotropium bromide 24–48 hours before, antihistamines 3 days before, and leukotriene modifiers 1 week before. Systemic corticosteroids should either be discontinued or reduced to the lowest possible dose [19, 22–24].

The oral challenge is administered by the oral route using specially dosed capsules with gradually increasing doses. When oral aspirin provocation was first introduced, it was administered using a protocol with doses spaced at 3-hour intervals and up to 3 days [25]. The modern provocation protocol typically begins with 20–40 mg of aspirin, gradually increasing the dose every 1–2 hours for a two-day period

according to the EAACI (European Academy of Allergy and Clinical Immunology) guidelines [19, 20] (Table 2). If no reactions occur within 3 hours after taking 325 mg of aspirin, the challenge is considered negative. Since reactions are usually not seen above 650 mg, increasing the dose beyond this dose is not recommended [15]. Faster protocols with 60-minute dose intervals [26, 27] have been reported, and another protocol has been reported in which aspirin challenge and desensitization are administered on the same day, with 90-minute dose intervals [28]. The generally reported provocative dose is 60–80 mg [29].

Table 2. Oral aspirin provocation test protocol.

| Step | Aspirin dose | Time after previous dose |
|------|-------------------------|--------------------------|
| 1 | 20–40 mg* | 60–90 minutes |
| 2 | 60–80 mg | 60–90 minutes |
| 3 | 100 mg | 60–90 minutes |
| 4 | 160–325 mg (final dose) | 60–90 minutes |

Total cumulative dose: ~340–545 mg, depending on the last step. Observation after final dose: at least 2 hours. * In high-risk patients, lower doses of aspirin can be introduced.

The test is considered positive if there is a 20% or greater decrease in FEV1 compared to baseline, or if extrapulmonary symptoms such as rhinorrhea, nasal congestion, urticaria/angioedema, abdominal pain, or anaphylaxis occur [30, 31].

Nasal aspirin provocation test (NAPT)

Nasal provocation may be preferred in patients with predominantly nasal symptoms or when oral or bronchial provocation is contraindicated, such as in severe asthma [1, 20]. It could be the first-choice method for highly sensitive patients, enabling other provocation routes for less sensitive individuals [19]. Although it is a safe and rapid method, its specificity and negative predictive value (NPV) are low, so oral or inhalation provocation should be performed whenever possible in patients with a negative test result [19]. It has the advantage of carrying a lower risk of systemic reactions compared to oral aspirin provocation [32].

The indications for intranasal aspirin provocation are:

1. It is suitable for diagnosing patients suspected of having N-ERD whose main symptoms are upper respiratory tract-related symptoms such as nasal congestion, rhinorrhea, and sneezing.
2. Identifying susceptible individuals: NAPT serves as an initial, reliable test to pinpoint the most susceptible individuals. If the result is negative, an oral provocation test can verify those who are less susceptible [1, 19, 20, 33].

Acetylsalicylic acid (ASA) derivatives are used as test materials. The most commonly used agent is L-lysine acetylsalicylate (L-ASA) solution [23]. L-ASA is a more water-soluble and less irritating salt form of ASA. It is applied locally to the nose during the procedure. In the USA and some non-European countries, L-ASA may be unavailable due to regulatory or manufacturing restrictions; in such cases, ketorolac, a potent COX-1 inhibitor, may be preferred for testing [34].

A period without acute nasal or sinus inflammation should be chosen for the test. Oral or topical antihistamines and leukotriene receptor antagonists (LTRAs) should generally be discontinued at least 3 to 7 days prior. Intranasal corticosteroids are usually discontinued 7 days prior to or continued at the lowest dose throughout the provocation. Oral corticosteroids should also be discontinued if possible [1, 20].

Before starting the test, the patient is kept in room air for 20–30 minutes, nasal hyperreactivity is then assessed using saline solution. 0.1 mL of L-ASA is administered via syringe, pipette, or dropper, targeting the inferior turbinate [32, 33, 35]. A cumulative aspirin equivalent dose of 18–20 mg is reached in an average of 1–4 doses. Although doses above 30 mg are thought to cause mucosal irritation, a recent study reported that increasing the maximum cumulative dose to 70 mg resulted in optimal sensitivity and

specificity, and was well tolerated [36]. Administering the full dose in a single dose is also an acceptable practice, rather than oral provocation.

For subjective evaluation, the patient's symptom scores of rhinorrhea, itching, and nasal congestion should be obtained using a visual analog scale. The use of objective measurement tools is recommended to improve the accuracy and reproducibility of nasal aspirin provocation testing [35]. Rhinomanometry is commonly used; a $\geq 100\%$ increase in nasal airway resistance relative to baseline is considered a positive response. When acoustic rhinomanometry is to be used, a reduction of 25% or more in nasal cavity volume indicates a positive test. Alternatively, a decrease of $\geq 40\%$ in maximum nasal inspiratory flow (PNIF) measurement is also considered positive [33].

Bronchial aspirin provocation test (BAPT)

Bronchial (inhalation) provocation testing has a similar sensitivity to oral provocation testing [19]. It is also safer due to its lower incidence of extra-bronchial symptoms and faster; the protocol is usually completed in 4 hours [32, 37]. Systemic reactions are generally not observed [5].

The bronchial aspirin provocation is indicated and is suitable for diagnosing patients suspected of having N-ERD whose main symptoms are of bronchial origin.

This method involves administering L-ASA in increasing doses using a dosimeter-controlled jet nebulizer [1]. A period when the clinical condition is stable, and FEV1 is above 70%, is selected for testing [20]. Short-acting B2 agonists should be discontinued 8 hours before, long-acting B2 agonists and tiotropium bromide 24–48 hours before, antihistamines 3 days before, and leukotriene modifiers 1 week before [20].

The placebo can be administered one day before or on the day of the test. The test begins with five breaths of 0.9% saline solution. FEV1 is measured after 10–20 minutes, and if the decrease is less than 10%, provocation is initiated. The L-ASA vials used in the test contain 1 g of lysine-aspirin, which is equivalent to 500 mg of ASA. The solution, prepared by dissolving L-ASA in saline, should be prepared immediately before the start of the test, as it remains stable at room temperature for up to 2 hours. Three increasing concentrations of lysine-aspirin (0.1 M, 1 M, and 2 M) are prepared for the provocation. The 2 M solution is made by dissolving 1 g of lysine-aspirin in 1.4 mL of saline. The 1 M and 0.1 M solutions are obtained by dilution of the higher-concentration stock solution [20]. FEV1 is measured at 10, 20, and 30 minutes after each dose. A decrease of 20% or more in FEV1, or the appearance of severe extrabronchial symptoms (rhinorrhea, nasal congestion, urticaria/angioedema, abdominal pain), is considered a positive test result. Table 3 summarizes the bronchial aspirin provocation protocol, adapted from Nizankowska-Mogilnicka et al. [20].

Table 3. Bronchial aspirin provocation protocol.

| Step | Lysine-aspirin concentration (M) | Inhalations | Aspirin dose (mg) | Cumulative dose (mg) |
|------|----------------------------------|-------------|-------------------|----------------------|
| 1 | 0.1 | 1 | 0.18 | 0.18 |
| 2 | 0.1 | 2 | 0.36 | 0.54 |
| 3 | 0.1 | 5 | 0.90 | 1.44 |
| 4 | 0.1 | 13 | 2.34 | 3.78 |
| 5 | 1 | 4 | 7.20 | 10.98 |
| 6 | 1 | 9 | 16.2 | 27.18 |
| 7 | 2 | 11 | 39.60 | 66.78 |
| 8 | 2 | 32 | 115.20 | 181.98 |

Each step is inhaled every 30 min. Increase the dose only if there is no significant reaction.

Alternative and less common approaches

Intravenous aspirin provocation stands out as a method with high sensitivity (93.5%) and specificity (100%). However, due to the risk of severe reactions, it should be performed under close monitoring in experienced centers. At present, it is more widely used in Japan. The appearance of severe extrabronchial

symptoms (rhinorrhea, nasal congestion, urticaria/angioedema, abdominal pain) is considered a positive test result [38, 39]. The overall aspirin forms and doses used in the different aspirin provocation tests are summarized in Table 4.

Table 4. Aspirin forms and doses used in different aspirin provocation tests.

| Provocation method | Aspirin form | Starting dose | Dose escalation | Maximum/Cumulative dose | Typical provocative dose |
|--------------------|---|---------------------------------------|---|---|------------------------------|
| OAPT | ASA capsule or tablet | 20–40 mg (5 mg in high-risk patients) | Gradual increase every 60–90 minutes | Final single dose 160–325 mg; cumulative dose ~340–545 mg | Usually 60–80 mg |
| NAPT | L-ASA solution (alternative: ketorolac) | 2–5 mg ASA equivalent | 1–4 incremental doses | Standard 18–20 mg; extended protocols up to 70 mg | Typically 10–20 mg |
| BAPT | L-ASA via nebulizer | 0.18 mg | Incremental cumulative doses every 30 minutes | 182 mg ASA equivalent | Often 1–10 mg |
| IAPT | ASA (IV formulation) | Protocol-dependent | Slow infusion or bolus according to protocol | Protocol-dependent | May be positive at low doses |

OAPT: oral aspirin provocation test; NAPT: nasal aspirin provocation test; BAPT: bronchial aspirin provocation test; IAPT: intravenous aspirin provocation test; L-ASA: L-lysine acetylsalicylate; ASA: acetylsalicylic acid.

Contraindications for aspirin provocation

General contraindications to oral, bronchial, and nasal provocation include clinical instability and uncontrolled asthma, both absolute contraindications. Some authors also consider an FEV1 value below 70% [1] or below 1.5 liters [15] as a contraindication. This restriction is in place to ensure the safety of the test. A history of severe anaphylaxis with aspirin or other NSAIDs is considered an absolute contraindication. Nasal provocation can be preferred in these situations [19]. A history of respiratory infection or asthma exacerbation within the preceding four weeks constitutes an additional contraindication [40]. Chronic renal failure or a history of gastrointestinal bleeding are contraindications due to the drug's systemic effects. Aspirin provocation should not be done during pregnancy or if the patient is undergoing beta-blocker therapy [19, 24].

Contraindications for nasal provocation are the presence of nasal cavity pathology that would affect the outcome of nasal provocation, such as massive nasal polyposis or septal perforation, or a history of upper respiratory tract infection involving the nasal cavity within the last 4 weeks [20, 41].

Predictive determinants of positive test results

The likelihood and severity of a reaction during an aspirin provocation test are influenced by the patient's underlying condition and disease control status at the time of testing. Risk factors can be broadly categorized into two groups: those that increase the likelihood of a positive reaction, indicating NSAID hypersensitivity, and those that either amplify the reaction's severity or contraindicate the test.

If the patient has a history of reactions to the same or different NSAIDs, the probability of a positive result from the provocation is over 80% [21]. In CRSwNP, the likelihood of a positive aspirin reaction increases with increasing Lund-Mackay score, a radiographic scoring system used to assess the degree of inflammation [42]. Similarly, the presence of eosinophilia also increases the risk of NSAID sensitivity [40].

Conditions that carry a higher risk of more severe reactions include uncontrolled asthma (FEV1 variability above 20%) or worsening of asthma (FEV1 below 80%) [33]. Patients between the ages of 30 and 40 may be at higher risk of severe reactions [15]. The failure to use protective medications, such as leukotriene-modifying drugs, during the procedure also increases the risk of severe reactions [15]. A comparison of aspirin provocation tests is shown in Table 5.

Table 5. Comparison of aspirin provocation tests.

| Provocation method | When to choose | Key advantages | Disadvantages |
|--------------------------------------|---|--|--|
| Oral aspirin provocation test | <ol style="list-style-type: none"> To confirm or exclude hypersensitivity in an unclear history. Gold standard for NSAID hypersensitivity. Verification of negative inhalation/nasal tests. Assessment before oral desensitization. | <p>Gold standard mimicking natural exposure.</p> <p>Highest sensitivity (80–90%).</p> | <p>Systemic reaction risk.</p> <p>Long duration (1–3 days).</p> <p>Contraindicated if FEV1 < 70%, pregnancy, severe anaphylaxis, or beta-blocker use.</p> |
| Bronchial aspirin provocation test | <ol style="list-style-type: none"> Diagnosis of NSAID hypersensitivity. Especially bronchial symptoms. | <p>Safer and faster than oral challenge.</p> <p>Comparable sensitivity (77–90%).</p> <p>Rare systemic reactions.</p> | <p>Lower NPV.</p> <p>A negative test requires confirmation with an oral aspirin challenge.</p> <p>Contraindicated if FEV1 < 70%.</p> |
| Intranasal aspirin provocation test | <ol style="list-style-type: none"> Upper airway symptoms. Alternative if oral/inhaled tests are contraindicated. Can be used as an initial safety test in sensitive patients. | <p>Safer and quicker.</p> <p>Preferred when oral/inhaled tests are contraindicated.</p> <p>Usually mild local reactions.</p> | <p>Lower sensitivity (80–86.7%).</p> <p>A negative test requires confirmation with an oral aspirin challenge.</p> <p>Contraindicated in massive nasal polyposis or septal perforation.</p> |
| Intravenous aspirin provocation test | Specialized centers to confirm NSAID hypersensitivity. | <p>Reported safe and efficacious in selected centers.</p> <p>High sensitivity (~93.5%).</p> | <p>Rarely used outside Japan.</p> <p>Risk of severe adverse reactions.</p> |

NSAID: non-steroidal anti-inflammatory drug; FEV1: forced expiratory volume in one second; NPV: negative predictive value.

Safety of the tests

Aspirin provocation tests have a favorable safety profile, especially when conducted in specialized centers. Adverse event rates vary by route of administration. In nasal aspirin provocation, reactions are primarily local, and systemic involvement is rare [36]. Mild nasal symptoms, such as congestion or rhinorrhea, are observed in about 40–80% of patients with a positive result [35, 41]. Reports of lower-airway symptoms are 5%, and severe bronchospasm or systemic reactions are 1%, making nasal challenge the safest method [41].

Bronchial lysine-aspirin provocation tests carry an intermediate risk profile compared with the other methods. A clinically significant fall in FEV1 ($\geq 20\%$) was observed in approximately 5–15% of patients, depending on asthma severity and the protocol used. Severe bronchospasm requiring systemic treatment occurs in fewer than 5% of cases, and life-threatening reactions are extremely rare (< 1%) [31, 43].

OAPTs are considered the diagnostic gold standard, but are associated with higher reaction rates due to systemic exposure. Approximately 20–30% of patients with suspected N-ERD experience respiratory reactions, including bronchospasm or combined upper and lower-airway symptoms [15]. Severe bronchospasm is reported in 9%, while anaphylaxis or hypotensive reactions remain uncommon (< 2–3%) in well-selected patients [15].

In general, when contraindications are observed and a standardized stopping protocol is adhered to, aspirin provocation tests are associated with a low frequency of serious adverse events, indicating their safe application in the diagnostic and phenotypic evaluation of N-ERD.

Aspirin challenge in the era of biologics

Biological drugs, anti-immunoglobulin E (IgE) or anti-IL-5 therapies, can suppress aspirin sensitivity in patients with N-ERD [44]. In N-ERD, the primary pathology is mediated by eosinophils, and an IgE-mediated pathway is not responsible for the clinical picture; however, omalizumab acts by reducing mast cell activation, thereby decreasing cysLT and PGD2 production [45]. Biologics that suppress type 2

inflammation (T2), such as dupilumab (anti-IL-4/13), have been reported to reduce nasal polyps and improve sense of smell by inhibiting this pathway. This may indirectly contribute to aspirin tolerance [46].

On the other hand, these treatments can prevent reactions during aspirin desensitization, allowing for silent desensitization [47]. This could make the procedure easier to perform in patients for whom desensitization is avoided due to the risk of reactions, and similarly, support an increase in the number of centers performing desensitization.

Conclusion

Current experience on the value of aspirin provocation tests in patients with N-ERD indicates that these tests are not merely confirmatory but are a cornerstone in the precision-based evaluation of N-ERD, enabling refined phenotyping, risk stratification, and individualized treatment planning in this complex and heterogeneous disease. In this sense, despite being associated with higher reaction rates due to systemic exposure, oral aspirin provocation captures the full spectrum of respiratory and extra-respiratory responses and therefore best reflects global disease severity and existing subphenotypes. However, in patients with dominant upper airway involvement, the NAPT seems to be the first option, considering its high diagnostic value and safety, if it is available. The higher safety profile of nasal challenge also allows this test to be a screening tool for determining the NSAID hypersensitivity component of N-ERD. BAPTs can also be used if the patient has mainly lower airway involvement. These phenotypic distinctions have direct therapeutic implications, influencing the selection of targeted treatments, including aspirin desensitization, biologic therapies, or surgical interventions. Therefore, defining the sub-phenotypes of the patients with N-ERD correctly by using the best methodology for aspirin provocation may allow for recommending better management options in these cases. Importantly, aspirin provocation tests have a favorable safety profile, especially when conducted in specialized centers.

Abbreviations

ASA: acetylsalicylic acid

ATAD: aspirin treatment after desensitization

BAPT: bronchial aspirin provocation test

COX-1: cyclooxygenase-1

CRSwNP: chronic rhinosinusitis with nasal polyps

EAACI: European Academy of Allergy and Clinical Immunology

FEV1: forced expiratory volume in one second

IgE: immunoglobulin E

L-ASA: L-lysine acetylsalicylate

LTRAs: leukotriene receptor antagonists

NAPT: nasal aspirin provocation test

NECD: non-steroidal anti-inflammatory drug-exacerbated cutaneous disease

N-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease

NIUAA: non-steroidal anti-inflammatory drug-induced urticaria/angioedema/anaphylaxis

NPV: negative predictive value

NSAID: non-steroidal anti-inflammatory drug

OAPT: oral aspirin provocation test

T2: type 2 inflammation

Declarations

Author contributions

NOA: Conceptualization, Investigation, Writing—original draft. GEÇ: Conceptualization, Investigation, Writing—review & editing, Supervision. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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