

Aspirin-Exacerbated Respiratory Disease: Clinical Disease and Diagnosis

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KEYWORDS

- Aspirin-exacerbated respiratory disease • Aspirin • Aspirin hypersensitivity
- Nonsteroidal anti-inflammatory drugs • Provocation test • Aspirin challenge

KEY POINTS

- Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome of intractable inflammation of both upper and lower airways, which is characterized by the presence of asthma, chronic eosinophilic rhinosinusitis, nasal polyps, and hypersensitivity reactions to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).
- Exposure to aspirin and other NSAIDs does not initiate the underlying inflammatory process but only exacerbates clinical manifestations of the disease.
- AERD develops according to a distinctive pattern, characterized by a sequence of symptoms: persistent rhinosinusitis, commonly with polyposis, followed by asthma, and then aspirin hypersensitivity.
- Asthma runs a protracted course despite avoidance of aspirin and other NSAIDs.
- Provocation tests with aspirin are the most reliable method to confirm the diagnosis of AERD.

INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) is a distinct clinical syndrome affecting both upper and lower airways, characterized by the presence of asthma, chronic eosinophilic rhinosinusitis, nasal polyps, and hypersensitivity reactions to cyclooxygenase 1 (COX-1) inhibitors, including aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Exposure to these drugs does not initiate the underlying inflammatory process but only exacerbates clinical manifestations of the disease.

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In line with the current classification, AERD belongs to cross-reactive types of hypersensitivity reactions to NSAIDs.¹

The association of aspirin sensitivity, asthma, and nasal polyposis was described for the first time in 1922 by Widal and colleagues.² This syndrome was widely popularized in the late 1960s when Samter and Beers^{3,4} described its natural history, and since then it was named *Samter's triad* or *the aspirin triad* (nasal polyps, asthma, and aspirin hypersensitivity). A fourth characteristic, chronic hyperplastic eosinophilic rhinosinusitis, was never mentioned in the description of "triad," but actually makes it a "tetrad"⁵ However, neither description is particularly useful, because linkage to the respiratory tract is not disclosed and the original description was not made by Samter in 1968 but rather by Widal in 1922. AERD is now the preferred descriptor in North America and is gaining worldwide acceptance.

PREVALENCE

The prevalence of aspirin hypersensitivity differs with respect to populations studied, diagnostic methods used, and criteria for defining hypersensitivity reactions. It affects 0.6% to 1.9% of the general population.^{6–8} The prevalence was found to range from 4.3% to 11% among adult patients with asthma assessed with questionnaires,^{6,7,9} and was even higher (21%) when provocation tests were used in patients with asthma and nasal polyposis and chronic rhinosinusitis.¹⁰ In patients with asthma, chronic rhinosinusitis, and nasal polyps, the prevalence of aspirin hypersensitivity confirmed through oral aspirin challenge was found to range from 30% to 40%.^{11,12} AERD is rare in children with asthma (2–5%) and is almost never seen before puberty.¹⁰ Women outnumbered men by a ratio of 2.3 to 1 in Europe,¹³ and 1.3 to 1 in the United States.¹⁴ Family history of aspirin hypersensitivity was found in 1% to 6% of cases.^{13,14} No racial or ethnic predilection to AERD was identified. The disease seems to be underdiagnosed in the population with asthma, because many patients who are aware of the risk of adverse reactions deliberately avoid NSAIDs. However, patients who experience mild NSAID-induced reactions do not associate them with drug ingestion or do not know that NSAIDs may cause asthma attacks.

NATURAL HISTORY

The first symptoms of AERD usually appear between the third and the fourth decade of life.¹⁵ In 2 large cohorts comprising 500 and 300 patients with AERD, the average ages of onset of the disease were 29 and 34 years, respectively.^{13,14}

AERD can develop in patients who already have rhinitis and/or asthma or in those who have never had any prior respiratory disease. The clinical presentation is similar worldwide.^{13,14} The disease develops according to a distinctive pattern, characterized by a sequence of symptoms: persistent rhinosinusitis, commonly with polyposis, followed by asthma, and then aspirin hypersensitivity. The first clinical manifestation is usually rhinitis, which is related to a flu-like infection. It is characterized by a watery discharge from the nose, nasal blockage, sneezing, and loss of smell. Rhinitis is perennial, difficult to treat, and progresses into a chronic hyperplastic eosinophilic rhinosinusitis often with nasal polyposis. Asthma is usually diagnosed 2 to 3 years later. At about the same time, the first unexpected adverse clinical reaction to aspirin or other NSAIDs occurs in patients who previously tolerated these drugs well. Some patients may have a diverse sequence of symptoms and NSAID-induced respiratory reactions, which are crucial for diagnosing AERD. Despite avoidance of aspirin and other NSAIDs, asthma runs a protracted course.

CLINICAL PRESENTATION

The typical adverse reaction to aspirin or other NSAIDs includes symptoms from upper and lower airways. The first symptoms appear within 30 to approximately 120 minutes after ingesting a full therapeutic dose of a causative drug. Bronchospasm of varying severity is usually accompanied by profuse rhinorrhea, nasal congestion, conjunctival irritation, ocular tearing, and, rarely, periorbital swelling. Some patients experience skin rash and erythema of head and neck. The reactions may differ in their severity, ranging from isolated rhinitis to life-threatening anaphylactoid reactions with hypotension and loss of consciousness.^{13,14} Individual patients experience nausea, stomach pain, and retrosternal pain. Vocal cord spasm can also occur during the reactions.

Asthma may vary in the degree of its severity. Some patients have mild or moderate disease. Others have severe chronic asthma requiring systemic corticosteroid therapy, frequent emergency department visits, or hospitalization from exacerbations. In the European cohort of 500 patients with AERD, 51% were treated with inhaled and oral corticosteroids, and a further 30% with high doses of inhaled corticosteroids to control their symptoms.¹³ In the last year preceding participation in the study, 24% received intravenous corticosteroids because of asthma exacerbations.¹³ Of the 300 patients with AERD in the United States, 77% were taking systemic corticosteroids in some pattern of use, such as every day, every other day, or as short courses, for treatment of exacerbations that occurred during the year before enrollment into the study.¹⁴ The results of the TENOR study (the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) revealed that patients with AERD demonstrated more-severe bronchial obstruction and were more likely to have had emergency department visits, unscheduled office visits, hospitalizations, and corticosteroid bursts in the previous 3 months because of asthma exacerbations compared with patients with severe asthma who tolerated aspirin well.¹⁶ In the European ENFUMOSA study, aspirin hypersensitivity was associated with more-severe cases of asthma.¹⁷ In another study from Poland, the presence of NSAID hypersensitivity was a significant risk factor for severe refractory asthma.¹⁸ AERD was highly prevalent among patients with near-fatal asthma in Japan.¹⁹ In the European AERD cohort, asthma was more poorly controlled in women, as evidenced by a significantly higher number of emergency interventions and hospital admissions for asthma exacerbations.¹³

Most patients experience severe nasal blockage, postnasal drip, and loss of smell. Chronic rhinitis progresses into chronic eosinophilic hyperplastic rhinosinusitis with nasal polyposis, which is especially aggressive, frequently fills all sinuses, and may even invade bone structures. In the European cohort, rhinitis was present in 82% and nasal polyps in 60% of this population.¹³ In the American cohort, almost all patients (99%) had nasal polyps.¹⁴ In the same group, abnormal sinus opacifications were seen on plain films or CT in 99% of patients.¹⁴ However, this high percentage may be biased by the high incidence of people referred for aspirin desensitization in that center. In another study, patients with AERD had a significantly higher rate of nasal polyps (90% vs 26%) and higher CT scores (16.9 vs 6.2) compared with patients with asthma who tolerated aspirin.²⁰ Chronic eosinophilic hyperplastic rhinosinusitis predisposes to secondary sinus infections, which may occur 5 to 6 times per year.¹⁴ Nasal polyps have a tendency to rapidly regrow, resulting in multiple polypectomies and sinus surgeries in many patients. An average number of these surgical interventions estimated in 2 large populations of patients with AERD ranged from 2.6 to 3.0 per patient.^{13,14}

In most cases, ingestion of aspirin or other NSAIDs by patients with hypersensitivity provokes both upper and lower airway response. However, a small subset of

individuals have isolated nasal symptoms.²¹ The reactions restricted to the upper respiratory tract during oral aspirin challenge were usually found in a mild and short-lasting disease.²²

AERD is usually accompanied by increased eosinophil counts in blood, induced sputum, and nasal lavage.^{15,23} However, particularly but not exclusively in patients treated with systemic corticosteroids, numbers of these cell counts can be within normal limits.

AERD can develop in patients who have both allergic and nonallergic rhinitis and asthma. The presence of atopy, determined by a skin prick test showing positive results to at least one aeroallergen, was found in 44% of this population.²⁴ In the same study, analysis of other definitions of atopy, including a combination of skin prick tests and history of atopy, specific and total IgE levels revealed that atopy was always more frequent in patients with AERD than in a general population without hypersensitivity to NSAIDs.²⁴ In a group of 103 German and Polish patients with AERD, positive skin prick test reactions to at least one aeroallergen were reported in 34%, increased levels of specific serum IgE (class ≥ 2) against common allergens in 34%, and total serum IgE levels greater than 100 IU/mL in 46%.¹³ Similarly, greater proportions of positive skin prick test reactions were found in the American cohort of 300 patients with AERD (66%), and in the TENOR study (92%).^{14,16}

RESPIRATORY REACTIONS TO ASPIRIN AND OTHER NSAIDS

Strong COX-1 Inhibitors

Patients with AERD typically experience cross-reactions to aspirin and NSAIDs that are strong COX-1 inhibitors with a predominant preferential activity against this enzyme (**Table 1**).^{25,26} The most common implicated analgesic both in Europe and the United States was aspirin, which elicited typical respiratory reactions in 80% of susceptible subjects.^{13,14} Ibuprofen (41%), naproxen (4%), and ketorolac (1%) were the next most common NSAIDs to induce respiratory reactions.¹⁴

Weak COX-1 Inhibitors

When given at a low dose (below 500 mg), acetaminophen (paracetamol), which is a weak COX-1 inhibitor, is safe in patients with AERD (**Table 2**). However, higher doses of this drug (≥ 1000 mg) elicit mild, easily reversed asthmatic reactions in some of these patients.²⁷ One study found that 34% of aspirin-sensitive patients with asthma reacted to acetaminophen in doses of 1000 to 1500 mg.²⁷ However, a recent meta-analysis revealed that only fewer than 2% of patients with asthma are likely to react to both acetaminophen and aspirin.¹⁰

Partially Selective COX-2 Inhibitors

Meloxicam and nimesulide are preferential COX-2 inhibitors, and are usually well tolerated by patients with AERD when given at lower doses (**Table 3**). However, they can elicit respiratory reactions at higher therapeutic doses, because these doses can also inhibit COX-1. These reactions appear in a minority of patients and tend to be mild.^{28–31}

Selective COX-2 Inhibitors

Rofecoxib, celecoxib, and the less popular valdecoxib, etoricoxib, parecoxib, and lumiracoxib—all called *coxibs*—are highly selective COX-2 inhibitors (**Table 4**). They are the most recent class of NSAIDs and are well tolerated by patients with AERD. Rofecoxib and valdecoxib, however, have been withdrawn from the market because of increased incidence of cardiovascular side effects. Celecoxib is the only remaining

Table 1
Strong COX-1 inhibitors^{a,b}

Generic Name	Brand Name
Acetylsalicylic acid	Aspirin
Benoxaprofen	Oralflex
Diclofenac	Cataflam, Voltaren
Diflunisal	Dolobid
Etodolac	Lodine
Fenoprofen	Nalfon
Flurbiprofen	Ansaid
Ibuprofen	Advil, Motrin, Rufen
Indomethacin	Indocin
Ketoprofen	Orudis, Oruvail
Ketorolac	Toradol
Meclofenamate	Meclomen
Mefenamic acid	Ponstel
Metamizole	Pyralginum
Nabumetone	Relafen
Naproxen	Aleve, Anaprox, Naprosyn
Oxaprozin	Daypro
Piroxicam	Feldene
Tolmetin	Tolectin

^a Cross-reactivity between these NSAIDs is expected.^b COX-2 inhibition only occurs at higher doses.

selective COX-2 inhibitor available in the United States. Outside the United States celecoxib, etoricoxib, parecoxib, and lumiracoxib are available. Many well-designed, placebo-controlled studies revealed that this group of drugs does not cross-react with aspirin and other COX-1 inhibitors when taken in therapeutic doses by patients with AERD. These results were obtained during oral challenges with rofecoxib,^{32–35} celecoxib,^{36–38} and the remaining coxibs.^{39,40} The results of these studies confirmed the hypothesis that inhibition of COX-1 is a critical event that triggers asthmatic attacks in patients with AERD. However, in some patients, hypersensitivity reactions to selective individual COX-2 inhibitors may occur.^{31,41,42} The responsible mechanisms are not understood. For these cases, IgE-mediated reactions are likely,^{43,44} and therefore the first full dose of a COX-2 inhibitor should be given to patients with AERD in a physician's office.

Table 2
Weak COX-1 inhibitors^{a,b}

Generic Name	Brand Name
Acetaminophen (paracetamol)	Tylenol
Salsalate	Disalcid
Azapropazone	Apazone
Choline magnesium trisalicylate	Trilisate

^a Usually well tolerated in AERD.^b Minimal COX-1 inhibition, without COX-2 inhibition at higher doses.

Table 3 Partially selective COX-2 inhibitors ^a	
Generic Name	Brand Name
Meloxicam	Mobic
Nimesulide	Aulin, Nimesil

^a Preferential COX-2 inhibition at lower doses but partial COX-1 inhibition at higher doses.

DIAGNOSIS

Accuracy of the History

History of asthma attacks and nasal reactions after ingestion of COX-1 inhibitors and typical clinical presentation are highly suggestive. However, exclusive reliance on a history is not advisable. A multicenter European study showed that 15% of patients were unaware of their NSAID hypersensitivity,¹³ and became informed of this diagnosis only after provocation tests with aspirin were performed. The indications that prompted physicians to perform these tests were the presence of asthma, nasal polyps, and/or sinusitis in patients avoiding aspirin and other NSAIDs. In one study 16% of consecutive patients with asthma and a prior history of NSAID hypersensitivity did not experience a reaction to aspirin during oral aspirin challenge.⁴⁵ Prior respiratory reactions could predict with some accuracy whether a positive oral provocation test result would occur, which also establishes the diagnosis of AERD. One study showed that patients with severe asthma attacks after ingestion of COX-1 inhibitors had a 100% chance of a positive result from an oral provocation test with aspirin.⁴⁶ Patients with a history of taking a NSAID and then having a mild or moderate prior asthma attack only once had a 73% to 79% chance of having AERD.⁴⁶ This chance increased to 89% when prior historical NSAID reactions occurred at least twice.⁴⁶ However, patients with nasal polyps, chronic rhinosinusitis, and asthma who were avoiding aspirin and other NSAIDs experienced positive results on oral aspirin challenges only 43% of the time.⁴⁶

Thus, AERD could be both underdiagnosed or overdiagnosed when relying exclusively on a history of associations between asthma attacks and ingestion of NSAIDs.

Provocation Tests with Aspirin

Provocation tests with aspirin are the most reliable method to confirm the diagnosis of AERD. No specific in vitro test exists. The following types of provocation tests exist,

Table 4 Selective COX-2 inhibitors ^a	
Generic Name	Brand Name
Celecoxib ^b	Celebrex
Etoricoxib ^c	Arcoxia
Lumiracoxib ^c	Prexige
Parecoxib ^c	Dynastat
Rofecoxib ^d	Vioxx
Valdecoxib ^d	Bextra

^a Preferential COX-2 inhibition at prescribed doses, without COX-1 inhibition.

^b Available worldwide.

^c Available outside the United States.

^d Removed from the world market in 2004 and 2005.

depending on a route of aspirin administration: oral, inhalation (bronchial), and nasal. In Japan and Korea, intravenous tests with aspirin are performed.⁴⁷ The principle of all tests is to deliver increasing doses (concentrations) of acetylsalicylic acid, followed by measurement of bronchial, nasal, ocular, and sometimes gastrointestinal or cutaneous reactions. Some patients react with a flush of their upper thorax. Associated urticaria, angioedema, vocal cord spasm, and hypotension also occur with less frequency.

Oral, inhalation, and nasal aspirin provocation tests do not differ significantly in sensitivity (89%–90%, 77%–90%, and 80%–86%, respectively) or specificity (93%, 93%, and 92.5–97.5, respectively).^{48–51} However, a negative predictive value is higher for oral tests than for inhalation challenges (77% vs 64%).^{48,49} Irrespective of the type of aspirin provocation tests used, they are performed based on 3 general indications:

- Suspicion of aspirin hypersensitivity based on a history of typical respiratory symptoms after ingestion of 1 or more COX-1 inhibitors.
- Suspected clinical presentation of AERD (eg, asthma, severe rhinosinusitis, and/or nasal polyposis) despite the lack of a clear history of prior NSAID reactions.
- As part of the aspirin desensitization process described in other articles elsewhere in this issue.

Safety Requirements and Circumstances for Performing Provocation Test with Aspirin

Patients undergoing oral or inhalation tests with aspirin should be in a stable clinical condition and their baseline forced expiratory volume in the first second (FEV₁) should be at least 70% of the predicted value.⁵² The tests must be performed in an outpatient or inpatient setting, under the direct supervision of experienced physicians, nurses, and skilled technicians. Emergency resuscitative equipment should be readily available. Nasal provocation tests are routinely performed in an outpatient clinic. It should be preceded by a rhinologic examination with anterior rhinoscopy to evaluate the presence of nasal polyps or any other abnormality that could interfere with the results of the test. Nasal inspiratory peak flow measurements can also be used and the equipment is not expensive.

In Europe, several asthma-controller drugs are temporarily discontinued before oral and inhalation tests (Table 5).⁵² Oral and topical corticosteroids should be continued; however, the dose of oral corticosteroids should not exceed 10 mg/d of prednisolone or an equivalent because it may blunt the response to aspirin.⁵³ In the United States, patients are allowed to continue not only inhaled and oral corticosteroids but also long-acting bronchodilator. Leukotriene modifiers are routinely continued to prevent hyperirritability of the airways.⁵⁴ Only antihistamines, short acting β_2 -agonists, and anticholinergics are discontinued for 24 hours before aspirin challenges.⁵⁴ Before

Table 5 Drug withdrawal before oral and inhalation provocation tests	
Drug	Time of Withdrawal
Short acting β_2 -agonists	6 h (8 h, if possible)
Ipratropium bromide	6 h (8 h, if possible)
Long acting β_2 -agonists	24 h (48 h, if possible)
Long acting theophylline	24 h (48 h, if possible)
Short-acting antihistamines	3 d
Leukotriene modifiers	At least 1 wk

nasal provocation tests, drugs that could blunt the response to aspirin should be also withdrawn (Table 6).⁵²

Oral Provocation Tests with Aspirin

Oral provocation tests with aspirin are regarded as the gold standard for diagnosing AERD. They are the most commonly performed, because the oral route mimics natural exposure and only a spirometer is required. Various protocols exist, which differ considerably in interval between administration of increasing doses of aspirin, total aspirin cumulative dose, and the criteria of the positivity of the test.

The oral provocation test worked up by the Task Force of HANNA (Hypersensitivity to Aspirin and other NSAIDs) together with the framework of GA2LEN Program, and accepted in Europe, takes 2 days.⁵² On the first day, 3 capsules of placebo consisting of saccharine lactate are administered at 1.5-hour intervals. On the second day, aspirin with exponentially increasing doses are administered at 1.5-hour intervals until a cumulative dose of 500 mg is reached (Fig. 1, Table 7). FEV₁ is measured before each dose of aspirin and every 30 minutes thereafter. The test is interrupted if FEV₁ decreases 20% or more from baseline values (a positive reaction), or if the maximum cumulative dose of aspirin (500 mg or 1000 mg) is reached without a decrease in FEV₁ of 20% or more and in the absence of nasoocular symptoms (negative reaction). The results of the test could be also regarded as positive when unequivocal symptoms, such as severe nasal congestion, rhinorrhea, ocular injection, periorbital swelling, and erythema of skin and/or thorax, appear even if the FEV₁ does not decline by 20%. For positive results on provocative challenge test, the dose of aspirin causing a 20% decline of a baseline FEV₁ is calculated (PD₂₀).

In the United States only oral aspirin provocation tests are available (Table 8).⁵⁴ The oral challenge protocol lasts 2 or 3 days. The following reactions to aspirin can be distinguished:

- 1. Nasoocular symptoms alone
- 2. Nasoocular symptoms and a 15% or greater decline in FEV₁ (classic reaction)
- 3. Lower respiratory reaction only (FEV₁ declines by >20%)
- 4. Laryngospasm with or without any of the first 3 reactions
- 5. Systemic reactions: hives, flushing, gastric pain, hypotension

Inhalation Provocation Test

Inhalation provocation tests are performed in several European centers.^{48,49,52} They are not used in the United States because lysine-aspirin has not been approved for use in humans by the U.S. Food and Drug Administration.

Table 6 Drug withdrawal before nasal provocation tests	
Drug	Time of Withdrawal
Nasal corticosteroids	7 d (or the lowest possible dose kept through the aspirin challenge)
Oral corticosteroids	7 d (or the lowest possible dose kept through the aspirin challenge)
Short acting antihistamines	24 h
Nasal α-mimetics	24 h
Oral α-mimetics	24 h
Leukotriene modifiers	At least 1 wk

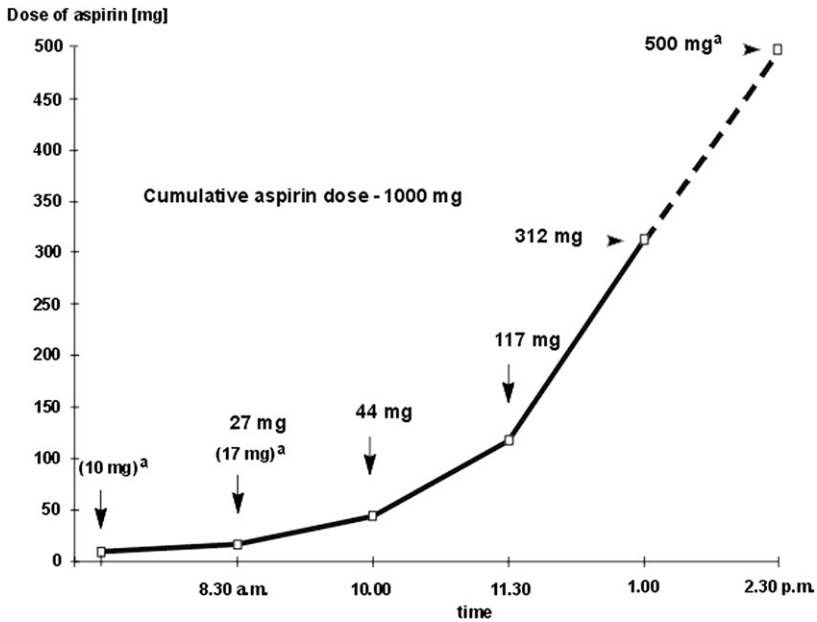


Fig. 1. Oral aspirin provocation test flowchart. ^a See [Table 7](#) for explanation. (Data from Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GALEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–8.)

For inhalation provocation tests, which last 1 day, increasing doses of lysine-aspirin solution (a soluble synthetic analog of aspirin) are administered through a dosimeter every 30 minutes, and FEV₁ is measured every 10 minutes ([Fig. 2](#)).⁵² The test is interrupted when FEV₁ decreases 20% or more from the baseline value or if strong extra-bronchial symptoms occur (positive reaction). If the maximum cumulative dose of lysine-aspirin (218 mg) is reached without any adverse symptoms, the results are

Table 7
The consecutive and cumulative doses of aspirin used in the oral provocation test (in Europe)

Consecutive Doses of Aspirin (mg)	Cumulative Doses of Aspirin (mg)
10 ^a	10
27	27
44	71
117	188
312	500
500 ^b	1000

^a Optionally, if a patient has a history of a severe reaction (severe dyspnea and/or anaphylactic shock) the provocation test should be started with 10 mg; the next dose of 17 mg is administered 1.5 hours later (ie, the 27-mg dose is divided into 2 doses for safety reasons).

^b Optionally, if a patient with a strong suspicion of aspirin hypersensitivity shows no reaction after the final dose of 312 mg of aspirin (cumulative dose 500 mg), the next dose 500 mg can be administered 1.5 hours later.

Data from Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GALEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–8.

Table 8
An oral provocation test used in the United States

Time	Day 1 ^a	Day 2 (or 1)	Day 3 (or 2)
8:00 AM	Placebo	20–40 mg	100–160 mg
11:00 AM	Placebo	40–60 mg	160–325 mg
2:00 AM	Placebo	60–100 mg	325 mg ^b

^a A placebo challenge can be conducted a week before; in patients whose baseline FEV₁ is the same as the previous best value and who have not used any rescue inhaler in the past week, the 1 day with placebo can be skipped.

^b Patients who have not reacted to 325 mg will not react to 650 mg; therefore, the test should be stopped after 325 mg and the results considered negative.

Data from Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 2009;9:155–63.

regarded as negative. In the case of a positive reaction, PD₂₀ of aspirin is calculated. The inhalation test is safer and faster to perform than the oral test, although it is less sensitive.⁴⁸ Its negative result does not totally exclude AERD. Therefore, in case of a suspicious history, it should be followed by an oral provocation test with aspirin.

Nasal Provocation Test

Nasal provocation tests are indicated in patients who cannot undergo oral or inhalation tests because of bronchial obstruction and severe asthma and in patients with typical symptoms of NSAID hypersensitivity exclusively in the upper airways.

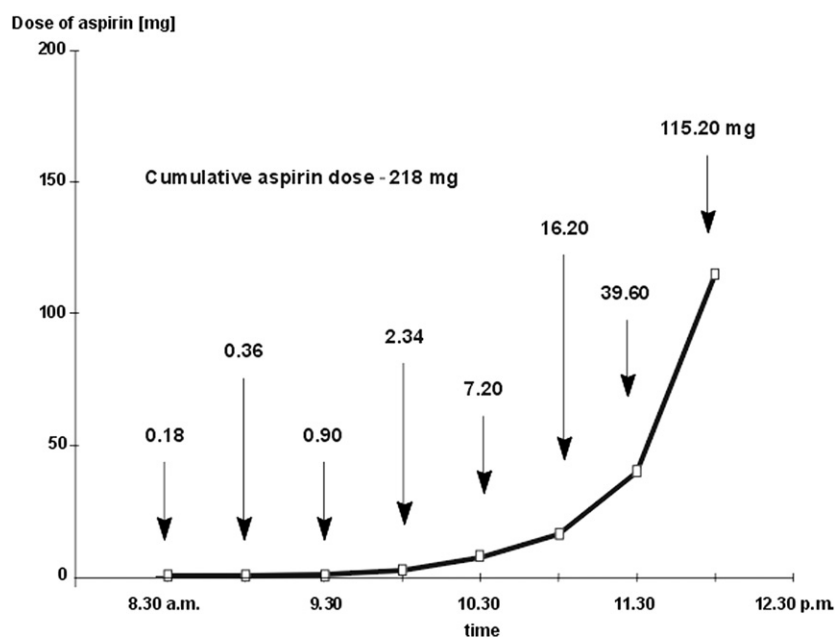


Fig. 2. Inhalation aspirin provocation test flowchart. (Data from Niżankowska-Mogilnicka E, Bochenek G, Mastalerz L, et al. EAACI/GALEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–8.)

Pulmonary function tests results are not a limitation for performance of nasal aspirin challenge tests.

After instillation of lysine-aspirin into the nostrils, the response is evaluated through recording nasal symptoms quantified with a visual analog scale and through using one of the following objective methods: acoustic rhinometry, active anterior rhinomanometry, or peak nasal inspiratory flow (PNIF).^{50–52} A positive reaction is defined as the appearance of nasal symptoms, such as rhinorrhea, nasal congestion, sneezing, and a 25% decrease of total nasal flow compared with a baseline value measured with acoustic rhinometry or a 40% bilateral drop of inspiratory nasal flow compared with a baseline value measured with rhinomanometry or PNIFmeter. In the United States, the alternative to lysine-aspirin is challenge is a solution of ketorolac delivered as a nasal spray.⁵⁵

The nasal provocation test is safe and rarely produces systemic reactions. However, a negative response does not rule out aspirin hypersensitivity and should be followed by oral aspirin provocation to make a definite diagnosis.

Patient Supervision After Provocation Tests

Positive bronchial reactions are relieved through inhalation or nebulization of short-acting β_2 -mimetics until FEV₁ returns within 90% of a baseline value. In the presence of more severe reactions, systemic corticosteroids are administered. Anaphylactic reactions require immediate intramuscular injections of epinephrine. Nasal obstruction is treated by topical α -mimetics. In the presence of severe nasal symptoms, oral corticosteroids may be useful.

Diagnosis In Vitro

Recently, the following in vitro tests were proposed to diagnose aspirin hypersensitivity in patients suspected of having AERD:

- Sulfidoleukotriene release assay, based on a potential capability of aspirin to induce LTC₄ release from peripheral blood leukocytes and, subsequently, on measurement of sulfidoleukotriene release.⁵⁶
- Basophil activation test, in which expression of cell surface molecule CD34 is measured on in vitro challenge with aspirin.⁵⁷
- 15-hydroxyeicosanoic acid (15-HETE) generation assay (ASPItTest) is based on aspirin triggering generation of 15-HETE, an arachidonic acid metabolite, only in patients with AERD.⁵⁸

Currently, none of these tests can be recommended for routine diagnosis of AERD, because their sensitivity and specificity have not been tested on large enough groups of patients, and results are inconsistent.^{1,59}

SUMMARY

AERD is a distinct clinical syndrome of intractable inflammation of both upper and lower airways, which is characterized by the presence of asthma, chronic eosinophilic rhinosinusitis, nasal polyps, and hypersensitivity reactions to aspirin and other NSAIDs. Exposure to aspirin and other NSAIDs does not initiate the underlying inflammatory process but only exacerbates clinical manifestations of the disease. AERD develops according to a distinctive pattern, characterized by a sequence of symptoms: persistent rhinosinusitis, commonly with polyposis, followed by asthma, and then aspirin hypersensitivity. Asthma runs a protracted course despite avoidance of

aspirin and other NSAIDs. Provocation tests with aspirin are the most reliable method to confirm the diagnosis of AERD.

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