ORIGINAL ARTICLE

Diagnosis of Aspirin-Induced Asthma Combining the Bronchial and the Oral Challenge Tests: A Pilot Study

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Abstract

Background: We investigated the usefulness of the bronchial challenge (BC) with lysine-acetylsalicylate (L-ASA) in the diagnosis of aspirin-exacerbated respiratory disease (AERD) using a protocol that combined both the oral challenge (OC) and the BC tests.
Methods: Adult asthmatic patients with suspected AERD who underwent BC with L-ASA were included in the study. If the BC result with L-ASA was negative, an OC was carried out to establish the diagnosis. AERD was ruled out if both the BC and the OC results were negative (nonresponders). Both responders and nonresponders were compared for age, gender, a personal or family history of atopy, underlying disease, current asthma treatment, and presence of nasal polyps. Six patients with asthma but no suggestive history of AERD were included as controls.
Results: Twenty-two patients completed the study. Ten patients tested positive to the BC and/or OC (responders), whereas 12 did not (nonresponders). Seven out of the 10 responders had a positive BC result and 3 a positive OC result. After BC, 4 patients had an early asthmatic response, 1 had a dual response, and 2 had isolated late responses. No significant differences were observed in the aforementioned variables between responders and nonresponders. The results of both challenges were negative in the 6 controls.
Conclusions: The BC had a high positive predictive value, was safe, and when negative, the subsequent OC did not result in any severe adverse reactions. The BC elicited an isolated late asthmatic response that has not been previously described in the literature.

Key words: Aspirin. Asthma. Diagnosis. Bronchial challenge. NSAIDS. Aspirin-exacerbated respiratory disease (AERD).

Resumen

Objetivos: Investigamos el valor diagnóstico de la técnica de la provocación bronquial especifica (PBE) con L-ASA (acetilsalicilato de lisina) en una muestra de pacientes con sospecha de enfermedad respiratoria exacerbada por aspirina (EREA), usando un protocolo que combina la PBE con la PO (provocación oral).
Métodos: Incluimos a todos los pacientes >18 años remitidos a nuestra Unidad de Provocaciones Bronquiales por sospecha de EREA. A todos se les realizó una PBE con L-ASA. Si era negativa, se confirmaba el diagnóstico mediante la PO. Se diagnosticaban de EREA si la PBE o la PO resultaba positiva (respondedores). Se recogió informacion sobre edad, sexo, antecedentes familiares y personales de atopia, enfermedad subyacente, existencia o no de poliposis, tratamiento de base ,y se compararon estas variables entre los dos grupos (respondedores y non-respondedores). Seleccionamos como controles 6 pacientes asmaticos sin historia de EREA.
Results: Finlizaron el estudio 22 pacientes. Diez fueron diagnosticados de EREA (respondedores), 7 mediante PBE positiva, 3 mediante PO positiva, mientras que en 12 pacientes se descartó la EREA (non-respondedores). De los con la PBE positiva, 4 pacientes tuvieron una respuesta asmática inmediata, uno dual y 2 una broncoconstriccion aislada tardía. No se encontraron diferencias significativas entre las variables arriba mencionadas. Tanto la PBE como la PO resultaron negativas en los 6 controles.
Conclusiones: La PBE resulto útil y segura para el diagnóstico de EREA, con un valor predictivo positivo muy alto, y cuando negativa la PO realizada después no exibió ninguna reacción severa. Obtuvimos una broncoconstricción aislada tardía, no descrita previamente en la bibliografía médica.

Palabras clave: Aspirina. Asma. Diagnóstico. Provocación bronquial. AINES. Enfermedad respiratoria exacerbada por aspirina (EREA).

Introduction

Acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) are a frequent cause of drug-induced asthma and urticaria, the two most common presentations of aspirin hypersensitivity [1].

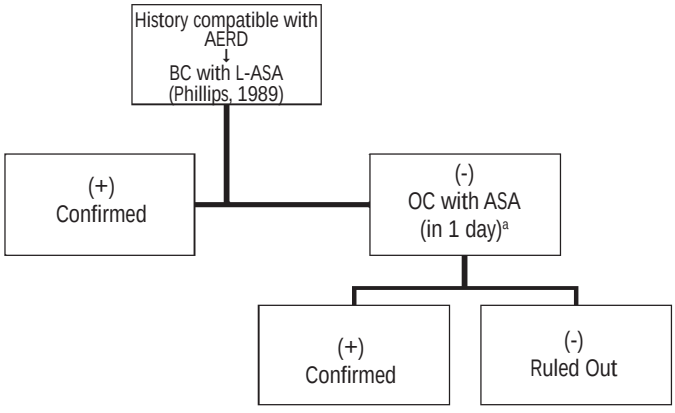
The condition traditionally known as Samter's triad (asthma, nasal polyposis, and allergy to aspirin) is currently referred to as aspirin-exacerbated respiratory disease (AERD) [2,3]. Patients with this condition usually suffer from chronic rhinitis and/or asthma, typically have nasal polyps and sinusitis, and their symptoms are seriously aggravated by NSAIDs.

In the absence of an in vitro test for the diagnosis of this entity, challenge tests are routinely performed to confirm or rule out AERD. There are 4 types of challenge test with aspirin: oral, bronchial, nasal (less used for diagnosing aspirin-induced asthma) [1,3-6], and intravenous, the latter used exclusively in Japan.

Bronchial challenge (BC) is generally performed with lysine-acetylsalicylate (L-ASA), a salt of acetylsalicylic acid that is more water-soluble than aspirin (40% vs 0.3%), nonirritant, and well tolerated when inhaled. The original procedure was described by Bianco [7] in 1977 and later improved by other authors [8-13].

Oral challenge (OC) is more time-consuming and protocols differ from one center to another. It elicits more extrabronchial reactions and severe, sometimes life-threatening bronchospasm [8,12]. The latest guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) and the Global Allergy and Asthma European Network (GA_2LEN) [14] recommend performing a BC or a nasal challenge in order to diagnose AERD. If the results are negative, an OC should be performed to confirm the diagnosis.

The objective of this cross-sectional study was to evaluate the sensitivity and specificity of BC with L-ASA and to assess the safety of a 1-day OC protocol in patients with suspected AERD.



[a] After at least 7 days from the BC

Figure 1. Diagnostic protocol for aspirin-exacerbated respiratory disease. ASA indicates acetylsalicylic acid; BC, bronchial challenge; OC, oral challenge.

Material and Methods

Patients

The study sample comprised all patients aged 18 years and older who were referred to our allergy clinic for suspicion of AERD between 2000 and 2007 and who gave their informed consent to undergo the challenges. All the patients had a history of rhinitis and/or physician-diagnosed asthma, which was moderate-severe in most cases, and some of them had associated chronic rhinosinusitis and nasal polyps. Patients who had contraindications for the technique were excluded [14], as were those who reported NSAID-induced symptoms other than asthma and/or rhinitis. The control group comprised 6 patients diagnosed with moderate persistent asthma and no nasal polyps or history of AERD. Before the challenge tests, all the participants gave their written informed consent and the study was approved by our institution's Ethics Committee.

On the day of the challenge test, patients had to have a baseline forced expiratory volume in 1 second (FEV_1) of at least 70% of predicted, and they needed to be clinically stable in order to proceed. They were told to withdraw oral corticosteroids and leukotriene modifiers 1 week before the challenge test, antihistamines 5 days before, long-acting $ß_2$-adrenergic agonists 48 hours before, inhaled corticosteroids 12 hours before, and short-acting $ß_2$-agonists 6 hours before.

All the patients underwent the BC first and, if the result was negative, they underwent an OC. The diagnostic protocol used is shown in Figure 1.The patients were considered responders (aspirin-intolerant asthmatics) if either the BC or the OC results were positive, and nonresponders (aspirin-tolerant asthmatics) if the results of both challenges were negative. The positivity criteria of the procedures are further specified below.

Clinical Characteristics

We collected clinical information regarding age, gender, family history of rhinitis or asthma, presence or absence of atopy (defined as 1 or more positive skin prick-test results with common aeroallergens), type of reaction with NSAIDs, drug involved in the reaction, underlying disease, and current treatment. In the end, we compared these variables between the responders and the nonresponders.

The mean age of the 22 selected patients was 42.5 years; 6 were men (27.3%) and 16 were women (72.7%). Six patients (27.3%) had a family history of rhinitis and/or asthma, and 12 (54.5%) were atopic (6 were sensitized to house dust mite, 10 to pollen, 1 to animal epithelia). Regarding their current asthma treatment, 13 were on regular inhaled corticosteroids combined with a long-acting bronchodilator, 1 was on inhaled corticosteroids, 5 were on short-acting bronchodilators as needed, and 3 were receiving no treatment at the time of the study. Aspirin was the NSAID involved in 13 patients' reactions (59.1%) (2 of these patients also reported respiratory symptoms with another NSAID), while in the remaining 9 patients (40.9%) the responsible NSAID was different.

The clinical characteristics of the study patients are summarized in Table 1.

Table 1. Demograhic Data and Clinical Characteristics of the Study Patients

Patient No.	Gender	Age	Family History	Atopy	Previous Diagnosis	Asthma Treatment	NSAIDs Involved
1	Male	37	No	Yes	R, A	3	ASA
2	Female	30	No	No	R	None	ASA
3	Male	41	No	No	R, A, P	CS+LAB	DCF
4	Female	60	No	Yes	R, A, AD	None	ASA
5	Male	28	R	Yes	R, A	CS+LAB	IBU
6	Female	35	No	Yes	R, A	CS+LAB	ASA
7	Female	51	No	No	R, A, P	CS+LAB	RFX
8	Female	45	No	Yes	R, A, P	SABA	MET
9	Female	20	No	Yes	R, A	None	IBU
10	Female	50	No	Yes	R, A	CS+LAB	IBU
11	Male	61	A	Yes	R, A	IC	ASA
12	Male	27	No	Yes	R, A, P	SABA	ASA
13	Female	60	No	No	R, A	CS+LAB	ASA
14	Female	38	No	No	R, A	CS+LAB	PCT
15	Female	45	A	Yes	R, A, P	CS+LAB	ASA
16	Female	29	No	No	R, A	SABA	ASA
17	Female	64	No	No	R, A, P	CS+LAB	ASA
18	Female	41	No	Yes	R, A,	SABA	IBU
19	Female	49	No	No	R, A, P	CS+LAB	ASA
20	Female	30	A	No	A	CS+LAB	KET
21	Female	32	R	Yes	R, A	SABA	ASA+MET
22	Male	62	No	No	R, A	CS+LAB	ASA+PCT

Abbreviations: AD, atopic dermatitis; A, asthma; ASA, acetylsalicylic acid; CS+LAB, corticosteroids and long-acting bronchodilators; DCF, diclofenac; IBU, ibuprofen; IC, inhaled corticosteroids; KET, ketorolac; MET, metamizole; P, nasal polyps; PCT, paracetamol; R, rhinitis; RFX, rofecoxib; SABA, short-acting ß$_2$ agonist.

BC With L-ASA

The BC test was performed using an electronic Spire Elektro dosimeter (Respiratory Care Center, Hameelinna, Finland) with an output of 0.45 µL and a nebulization time of 0.6 seconds. Spirometry testing was performed according to the recommendations of the American Thoracic Society [15] using a SpiraAnalyzer ST-75 spirometer (Fukuda Sangyo, Nagareyama, Japan).

We followed the modified method of Phillips et al [16], which consists of inhalations of serial doubling concentrations of L-ASA. For this, we dissolved 2 vials of L-ASA (Inyesprim, Grupo Grunnenthal, Madrid, Spain) (1800 mg) in 5 mL of distilled water, to obtain a concentration of 360 mg/mL, which equals 200 mg of aspirin. Then, successive 2-fold dilutions were obtained by adding normal saline (0.9% sodium chloride) to obtain L-ASA concentrations of 180 mg/mL, 90 mg/mL, and 45 mg/mL. The patient inhaled the aerosolized L-ASA following the dosimeter protocol presented in Table 2. The challenge was preceded by 5 inhalations of 0.9% saline solution. If the FEV_1 had not dropped >10% from baseline after 20 minutes, the BC with L-ASA was started. Increasing doses of L-ASA were inhaled every 30 minutes and the FEV_1, forced vital capacity (FVC), and peak expiratory flow (PEF) were measured 10, 20, and 30 minutes after each dose. The BC was interrupted if the FEV_1 dropped by ≥20% of the postsaline FEV_1, if extrabronchial symptoms appeared, or when the final dose had been reached. Then, PEF and FEV_1 were measured

Table 2. Bronchial Challenge Test With L-ASA

L-ASA (mg/mL) Concentration	No. of Inhalations	Milligrams of L-ASA Inhaled	Milligrams of L-ASA Accumulated
45	1	0.405	
45	5	2.025	2.43
90	5	4.05	6.48
180	5	8.1	14.58
180	10	16.2	30.78

Abbreviations: L-ASA, lysine acetylsalicylate.

1 hour and 2 hours after the end of the BC. The patient self-measured PEF every 2 hours at home, except when asleep, until 24 hours later, when a new spirometry test was performed at the hospital laboratory.

The BC took approximately 4 hours. If bronchospasm appeared during or after the BC, it was treated with 200 µg of salbutamol, which was repeated 20 minutes later if necessary. After another 20 minutes, if no significant improvement was observed, intravenous methylprednisolone at 40 mg was administered. Patients were admitted to hospital if the initial spirometric values were not reached within the following 2 hours. In the case of a positive BC, the dose of L-ASA causing a 20% fall in FEV_1 was calculated in milligrams by interpolation of the last 2 concentrations.

The BC result was considered positive if the patient presented an immediate response with a ≥20% drop in FEV_1, a prolonged immediate asthmatic response, a dual response, or extrabronchial symptoms. The BC was regarded as positive if the patient only presented a late asthmatic response, defined as a ≥20% drop in PEF starting any time between 4 hours and 24 hours after the BC or by the development of intense bronchial symptoms (wheezing, shortness of breath, chest tightness) that were reversible with bronchodilators along with an increase in PEF of ≥20% postbronchodilator. This type of asthmatic reaction (isolated late) was subsequently confirmed by means of an OC performed at least 1 week apart from the previous challenge.

The BC result was considered negative if the maximum dose was reached and no drop in FEV_1 or PEF ≥20% was observed in the following 24 hours.

Table 3. Oral Challenge With Aspirin[a]

Time	Dose, mg
8:30 AM	Placebo
9:00 AM	250
11:00 AM	500

[a] If within 120 minutes after the 250-mg dose had been administered the patient showed no extrabronchial or bronchial symptoms, with a drop of peak expiratory flow (PEF) of <15% or forced expiratory volume in 1 second <20%, 500 mg of acetylsalicylic acid was administered. In the case of a 15%-20% drop in PEF, the next dose was postponed for 60 minutes and PEF was monitored every 15 minutes. In the case of no significant recovery, the dose was repeated.

Oral Challenge Test With Aspirin

The OC was performed in patients with a negative BC result. We were able to conduct this test safely in 1 day, under the continuous supervision of trained personnel, with cardiopulmonary resuscitation equipment available. We started with a dose of placebo, followed by aspirin. The rapid OC protocol is presented in Table 3. In the particular cases of the 2 patients who developed an isolated late response in the BC, we followed the 3-day protocol of Stevenson et al [3] in order to confirm the AERD diagnosis.

The development of bronchial symptoms (wheezing, dyspnea), naso-ocular symptoms (rhinorrhea, nasal congestion,

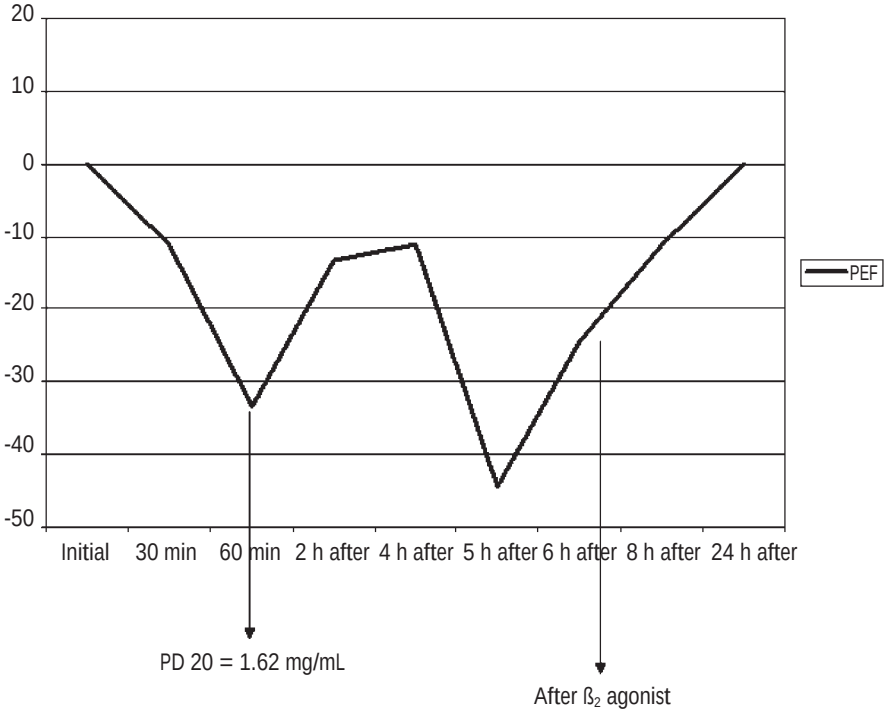


Figure 2. Dual asthmatic response.

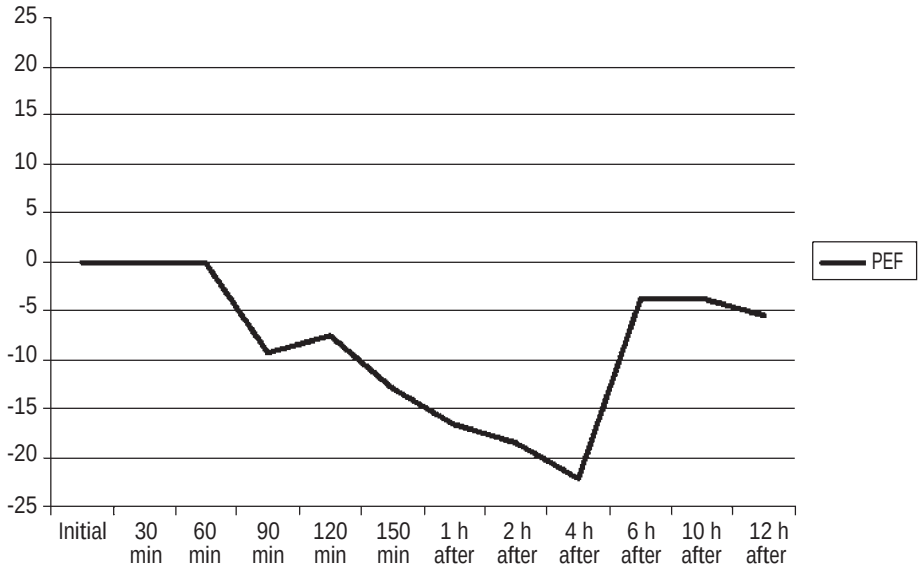


Figure 3. Late asthmatic response after bronchial challenge with L-ASA lysine acetylsalicylate. PEF indicates peak expiratory flow.

tearing, conjunctival injection, periorbital edema) and systemic symptoms (urticaria, dizziness, hypotension, vomiting) was carefully monitored.

The OC was interrupted if a ≥20% drop in FEV_1 or PEF occurred, if extrabronchial symptoms appeared, or when the maximum dose was reached.

The OC result was considered negative when the maximum dose was administered and no extrabronchial symptoms or a ≥20% drop in FEV_1 or PEF appeared during the following 4 hours.

Statistical Analysis

Comparisons between groups were carried out using the nonparametric Mann-Whitney test. Categorical variables were compared using the χ^2 test with a Yates correction. A *P* value of less than .05 was considered significant. All tests were performed using SPSS version 11.0. The statistical analysis was supervised by a professional statistician.

Results

Of the initial 27 patients included, 5 did not complete the study (they did not give their informed consent for the OC after a negative BC result). Therefore, the study protocol was completed in 22 asthmatic patients with suspected AERD (6 had associated nasal polyps). Of these 22 patients, 10 (45.5%) were diagnosed with AERD (7 by a positive BC, and 3 by a positive OC), and in the remaining 12 patients (54.5%) AERD was ruled out.

BC With L-ASA

BC was positive in 7 patients: 4 had an immediate response, 1 a dual response (Figure 2), and 2 an isolated late asthmatic response (one with a 23% drop in PEF 6 hours after the BC [Figure 3], and the other with dyspnea, wheezing, and chest tightness—reversed with a bronchodilator—and a 21% increase in PEF). In both patients, the diagnosis was

Table 4. Results of the Provocations

Patient Number	Bronchial Challenge With L-ASA (PD20 in mg)	Oral Challenge With ASA
1	Negative	AP
2	Negative	R
3	Negative	R
4	IAR (19.8)	NP
5	IAR (11.7)	NP
6	IAR (2.7)	NP
7	Negative	Negative
8	Negative	Negative
9	Negative	Negative
10	Negative	Negative
11	LAR	A
12	Negative	Negative
13	Negative	Negative
14	DAR (1.62)	NP
15	Negative	Negative
16	Negative	Negative
17	Negative	Negative
18	Negative	Negative
19	Negative	Negative
20	Negative	Negative
21	IAR (30.78)	NP
22	LAR	A

Abbreviations: A, asthma; AP, anaphylaxis; ASA, acetylsalicylic acid; DAR, dual response; IAR, immediate asthmatic response; LAR: late asthmatic response; L-ASA, lysine acetylsalicylate; NP, not performed; R, rhinitis.

confirmed by an OC with aspirin, which eventually yielded positive results (bronchospasm). The BC proved to be safe, had a specificity and a positive predictive value of 100%, with a lower sensitivity (70%) and negative predictive value (80%), justified by the failure in diagnosing rhinitis.

OC With Aspirin

The 15 patients with a negative BC result underwent the OC with aspirin (Table 3). The OC was negative in 12 patients and positive in 3 (2 patients developed rhinitis and 1 had angioedema and rhinitis without bronchospasm). These reactions were easily controlled with methylprednisolone and diphenhydramine. None of the patients required hospitalization and the symptoms ceased in less than 2 hours, except for 1 patient whose nasal congestion lasted for almost 12 hours.

The results of both the BC and the OC are shown in Table 4.

We found no statistically significant differences for the variables studied (age, gender, family history of rhinitis or asthma, presence or absence of atopy, type of reaction with NSAIDs, NSAIDs involved, underlying disease, and current treatment) between the responders and the nonresponders.

Both the BC and the OC were negative in the 6 controls.

Discussion

In this study, AERD was confirmed in 45% of the suspected cases, a percentage that is lower than that reported in other publications (66%-97%) [16-18]. The fact that there were no differences between the clinical characteristics of the responders and nonresponders could be due to the sample size, but also to the waning of the aspirin-induced respiratory symptoms in the nonresponders, as described elsewhere [19], or to prolonged treatment with inhaled corticosteroids [20] (10 of the patients who had a negative BC result were treated with inhaled corticosteroids alone or in combination with long-acting $ß_2$-adrenergic agonists). Given the widespread use of NSAIDs, our results support the need to confirm the diagnosis of AERD.

The 7 patients who had a positive BC experienced mild bronchospasm, which was easily reversible with inhaled $ß_2$-adrenergic agonists. We did not observe any immediate-prolonged response [10], whereas a dual asthmatic response [9] developed in one patient, and an extrabronchial reaction [12,13] was observed in another. Interestingly, in 2 patients we observed isolated late asthmatic responses, which were documented by PEF recordings and subsequently confirmed by a positive OC (bronchoconstriction).

One of the reasons for obtaining late responses and positive OC results after a negative BC could be that the total cumulative dose of inhaled L-ASA was insufficient to trigger immediate responses, as has been previously suggested [10,12]. On the other hand, if the cumulative dose of 181 mg was reached [14], there might be a higher risk of systemic reactions, as reported by Makowska et al [21].

When the BC was negative, it reassured the safety of OC with aspirin. The 3 patients in whom the OC was positive had neither bronchospasm nor severe systemic reactions, so the 1-day protocol proved to be safe. Two patients experienced rhinitis only, indicating that the BC might not be sufficiently sensitive for diagnosing patients who only experience rhinitis symptoms with NSAIDs. Dahlén et al [13] have also reported 2 patients who suffered nasal symptoms and no bronchospasm after the OC, but did not experience symptoms with the BC, which was negative.

Only 2 studies have compared both challenge protocols [12,13], finding a similar specificity but higher sensitivity for the OC, as the BC usually fails to diagnose rhinitis.

We found the BC extremely useful for diagnosing AERD. The protocol we developed allowed us to establish an accurate diagnosis in a shorter time, with fewer risks for the patient and with less use of medical resources. Furthermore, the BC had a high negative predictive value in this study (80%), as reported by other authors [8,10,13]. Therefore, we consider that the BC with L-ASA could be regarded as a first diagnostic approach in patients with suspected AERD.

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