

## Review article

## EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity

**Abstract:** Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common causes of adverse drug reactions. Majority of them are of the hypersensitivity type. The two frequent clinical presentations of aspirin hypersensitivity are: aspirin-induced bronchial asthma/rhinosinusitis (AIA/R) and aspirin-induced urticaria/angioedema (AIU). The decisive diagnosis is based on provocation tests with aspirin, as the *in vitro* test does not hold diagnostic value as yet. Detailed protocols of oral, bronchial and nasal aspirin provocation tests are presented. Indications, contraindications for the tests, the rules of drug withdrawal and equipment are reviewed. Patient supervision and interpretations of the tests are proposed.

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Key words: aspirin; aspirin challenge; aspirin-induced asthma/rhinitis; aspirin-induced urticaria; hypersensitivity.

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Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common causes of adverse drug reactions (1). Majority of them are of the hypersensitivity type.

The two frequent clinical presentations of aspirin hypersensitivity are: aspirin-induced bronchial asthma/rhinosinusitis (AIA/R) and aspirin-induced urticaria/angioedema (AIU). Recent data point to emerging basic similarities at the biochemical level between these two distinct clinical syndromes (2). It was proposed 30 years ago that aspirin-precipitated reactions result from inhibition of cyclooxygenase (COX) by aspirin-like drugs in the

airways or in the skin of the hypersensitive patients (3). This basic COX theory has been restricted recently to COX-1 enzyme. Inhibition of COX-1 diminishes the synthesis of prostaglandin E<sub>2</sub>, normally acting as a brake on the production of cysteinyl leukotrienes (cysLTs) (4). On the other hand, patients with aspirin hypersensitivity generally tolerate well NSAIDs which are highly selective inhibitors of COX-2 (5). Another distinguishing feature of aspirin hypersensitivity is the upregulation of the 5-lipoxygenase pathway, resulting in cysLT overproduction (6–8).

The prevalence of aspirin hypersensitivity in the general population ranges from 0.6% to 2.5% and in

asthmatics from 4.3% to 11% (9–11). In the last meta-analysis the prevalence of AIA in an adult population of asthmatics was reported to be as high as 21% when provocation tests were used for diagnosis (12). Under-diagnosis of aspirin hypersensitivity points to the necessity of more extensive use of aspirin challenge tests in medical practice. The *in vitro* test does not hold diagnostic value as yet; work continues to develop one (13, 14).

The oral challenge test with aspirin was introduced into clinical practice in the early 1970s (3, 15). Over the following years it was validated and used more frequently (16–22). The inhalation test for the diagnosis of aspirin hypersensitivity in subjects with asthma was introduced into clinical practice in 1977 (23). In the following years its use became popular (18, 19, 24–26). This challenge is safer and faster to perform than the oral test, although it is slightly less sensitive. Unlike oral challenge, it usually does not produce systemic reactions. A nasal provocation test was introduced in the late 1980s (27–31). It is recommended particularly for patients with predominantly nasal symptoms and those in whom oral or inhalation tests are contraindicated because of the asthma severity. As the negative predictive value is lower than in the other two tests, a negative nasal challenge should be followed, whenever possible, by the oral or inhalation test.

Establishing a diagnosis of aspirin hypersensitivity is of utmost importance. It provides the patient with a long list of common drugs that must be avoided because of the high risk of a life-threatening reaction and indicates which NSAIDs can be taken safely. Detailed protocols of aspirin provocation tests for the diagnosis of aspirin hypersensitivity are proposed below.

Aspirin (acetylsalicylic acid) provocation tests should be carried out in males and females with a history of prior hypersensitivity reaction to aspirin and/or other NSAIDs, or when a subject is suspected of suffering from AIA/R or AIU.

In order to diagnose AIA/R the following challenge procedures (tests) should be used:

- 1 Oral aspirin challenge (see Oral, single-blind, placebo-controlled diagnostic challenge tests with aspirin).
- 2 Bronchial (inhalation) L-lysine-aspirin (L-ASA) challenge (see Single-blind, placebo-controlled bronchial aspirin challenge).
- 3 Nasal L-ASA challenge (see Single-blind, placebo controlled nasal aspirin challenge).

In order to diagnose AIU, a modified oral aspirin challenge should be used (see Single-blind, placebo-controlled oral aspirin challenge test in patients suspected of aspirin-induced urticaria).

The sensitivity of the oral aspirin test (when decrease in forced expiratory volume in 1 s ( $FEV_1$ ) > 20% and/

or extrathoracic symptoms were used as endpoints – severe rhinorrhoea, nasal congestion, etc.) was 89%, and the specificity reached 93% (19). The sensitivity and specificity of bronchial challenge with aspirin was 77% and 93%, respectively (19). The negative predictive value was higher when the oral aspirin challenge was used (77% vs 64%) (19). According to Dahlén and Zetterström (20) the sensitivity of bronchial challenge with L-ASA was comparable with the sensitivity of oral aspirin challenge (both 90%). It should be noted, however, that in those two studies the total cumulative aspirin dose was 500 mg. We propose that in certain cases the total cumulative dose should be increased to 1000 mg (for details see below).

Milewski et al. (30) and Alonso-Llamazares et al. (32) found that the specificity of nasal challenge with lysine-aspirin reached 95.7% and 92.5% respectively, whereas its sensitivity was 86.7% and 80%, respectively. The predictive value of a negative result of L-ASA nasal challenge was 78.6% and 89.2%, respectively (30, 32). Subjects should give written informed consent to participate in aspirin challenges after the actual nature of the procedures has been thoroughly explained to them by the attending physician.

#### **Oral, single-blind, placebo-controlled diagnostic challenge (provocation) tests with aspirin**

##### General considerations

- 1 Oral challenges have to be carried out under the direct supervision of a physician and technicians skilled in performing provocation tests with aspirin.
- 2 Emergency resuscitative equipment should be readily available. Patients should have an intravenous line attached.
- 3 The patients should be in a stable clinical condition.
- 4 Baseline  $FEV_1$  should be at least 70% of the predicted value for oral challenges with aspirin.

##### Contraindications for oral aspirin challenges:

- 1 A history of very severe anaphylactic reactions precipitated by aspirin or other NSAIDs (nasal aspirin challenge should be considered in any such case).
- 2 Severe disease of the heart, digestive tract, liver, kidney.
- 3 Infection of respiratory tract within 4 weeks prior to the challenge.
4. Pregnancy.
- 5 Current treatment with  $\beta$ -receptor blocker.

Drug withdrawal before oral aspirin challenge procedures:

Short-acting $\beta_2$ -agonists	6 h (8 h, if possible)
Ipratropium bromide	6 h (8 h, if possible)
Long-acting $\beta_2$ -agonists	24 h (48 h, if possible)
Long-acting theophylline	24 h (48 h, if possible)
Tiotropium bromide	24 h (48 h, if possible)
Short-acting antihistaminics	3 days
Cromolyn sodium	8 h
Nedocromil sodium	24 h
Leukotriene modifiers	At least 1 week

If regular treatment with oral corticosteroids is required the dose should not exceed 10 mg of prednisolone or equivalent. The dose of inhaled (bronchial) and local (nasal) corticosteroids should be as low as possible and should be kept stable throughout the duration of the challenge. Any therapy with corticosteroids should be carefully recorded, as they may blunt any response to aspirin (16).

*Aspirin.* Acetylsalicylic acid in a powder form, administered in gelatin capsules prepared by the hospital pharmacy.

*Placebo.* Saccharin lactate administered in gelatin capsules. The capsules should have an identical appearance to those containing acetylsalicylic acid.

*Challenge protocol – day 1 (placebo).* Forced expiratory volume in 1 s is measured and the baseline value is chosen as the best of three efforts (which do not differ by more than 10%). The challenge is started if the baseline FEV<sub>1</sub> is at least 70% of the predicted value for the patient. Three (or optionally four) capsules of placebo are administered at 1.5–2 h intervals. Forced expiratory volume in 1 s is measured every 30 min and the values are allowed to vary by < 15% from baseline. If a greater variation in FEV<sub>1</sub> occurs the patient is deemed in an unstable clinical condition and therefore is excluded from any further challenge.

*Challenge protocol – day 2 (aspirin).* Forced expiratory volume in 1 s is measured and the baseline value is chosen as the best one of three consecutive efforts. The challenge commences when the baseline FEV<sub>1</sub> is at least 70% of the predicted value.

Usually four exponentially increasing doses of aspirin (27, 44, 117, 312 mg) are administered every 1.5–2 h until a cumulative dose of 500 mg is reached (Table 1).

If a patient has a history of a severe reaction (very severe dyspnoea and/or anaphylactic shock) after aspirin or other NSAIDs the test is commenced with 10 mg of aspirin and the next dose of 17 mg is administered 1.5–2 h later, i.e. the 27 mg dose is divided into two doses for safety reasons (Table 1).

If a patient with a very strong suspicion of aspirin hypersensitivity shows no reaction after the final dose of

Table 1. The consecutive and cumulative doses of aspirin used in oral aspirin challenge

Consecutive doses of aspirin (mg)	Cumulative doses of aspirin (mg)
10*	10
<b>27</b>	<b>27</b>
<b>44</b>	<b>71</b>
<b>117</b>	<b>188</b>
<b>312</b>	<b>500</b>
500*	1000

\*Optionally (see the text for explanation).

312 mg aspirin (cumulative dose 500 mg), another capsule containing 500 mg of aspirin may be administered 1.5–2 h following the preceding dose; the cumulative dose in that case will be equivalent to 1000 mg of aspirin (Table 1, Fig. 1). The consecutive and cumulative doses of aspirin are listed in Table 1. Forced expiratory volume in 1 s is measured before each consecutive dose of aspirin and subsequently every 30 min, i.e. at 30, 60 and 90 (or at 30, 60, 90 and 120) min thereafter.

Patients are also observed for the following clinical symptoms:

- 1 Bronchial (bronchospasm, tightness of chest, wheezing).
- 2 Upper airway (rhinorrhea, nasal congestion).
- 3 Other reactions (ocular injection, periorbital swelling, erythema of the skin of the upper thorax and face, nausea, stomach cramps, etc.).

All these symptoms should always be diligently recorded.

The challenge is promptly interrupted if a decrease in FEV<sub>1</sub>  $\geq$ 20% of baseline occurs (a positive reaction), or when the maximum cumulative dose of aspirin is reached without a fall in FEV<sub>1</sub>  $\geq$ 20% and the symptoms of aspirin

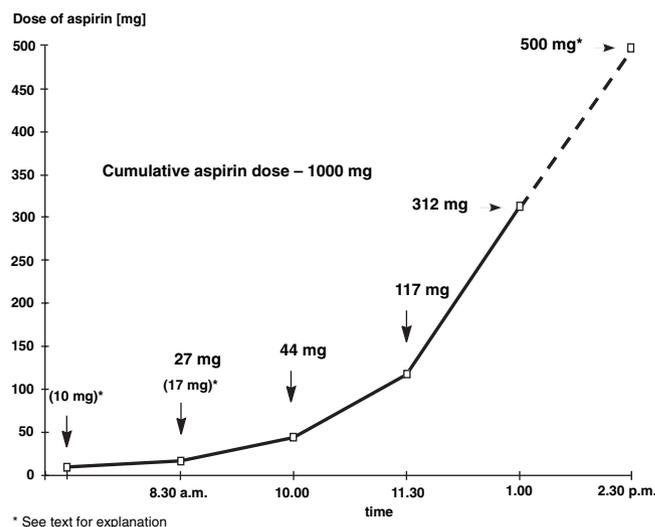


Figure 1. Oral aspirin challenge flowchart.

hypersensitivity do not appear (a negative reaction). The exact time of a fall in FEV<sub>1</sub> ≥20% should be recorded.

The provocative dose causing a 20% fall in baseline FEV<sub>1</sub> is calculated (PD<sub>20</sub>). The lowest FEV<sub>1</sub> out of three measurements (at 30, 60 and 120 min) obtained after each dose is plotted against the log<sub>10</sub> cumulated dose of aspirin to obtain a dose-response curve. The PD<sub>20</sub> is calculated by the linear extrapolation from this curve.

The oral aspirin test could also be regarded as positive when severe extrabronchial symptoms of aspirin hypersensitivity appear (e.g. profound rhinorrhea and nasal blockade even if FEV<sub>1</sub> fall does not exceed 20%). The challenge is then stopped.

**Single-blind, placebo-controlled bronchial (inhalation) aspirin challenge**

General consideration

As for oral aspirin challenges (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin).

Contraindications for bronchial challenges

As for oral aspirin challenges (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin).

Drug withdrawal before bronchial aspirin challenge procedures

As for oral aspirin challenges (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin).

*Lysine-aspirin.* Crystalline lysine-aspirin (Aspisol™; Bayer, Leverkusen, Germany) is provided in vials containing 1 g of lysine-aspirin, which corresponds to 500 mg of acetylsalicylic acid. The solutions are prepared fresh just before the challenge, by dissolving the crystalline lysine-aspirin in 0.9% sodium chloride (saline).

Three incremental solutions of lysine-aspirin are used: 0.1, 1 and 2 M. In practice the 2 M solution is obtained by dissolving one vial (1 g of lysine-aspirin) in 1.4 ml of saline, which gives 720 mg/ml of lysine-aspirin, i.e. 360 mg/ml of aspirin. The 1 M solution is obtained by adding 1 ml of saline to 0.5 ml of the 2 M solution or by dissolving 1 g of lysine-aspirin in 2.8 ml of saline. The 0.1 M solution is obtained by adding 0.9 ml of saline to 0.1 ml of the 1 M solution.

The solutions should be kept refrigerated as they remain stable only for 2 h after preparation. Crystalline lysine-aspirin (Aspisol™) is stable and may be kept at room temperature for a prolonged period of time.

*Equipment for nebulization.* Lysine-aspirin is administered by a dosimeter-controlled jet-nebulizer (Spira Electro 2, Respiratory Care Center, Hameenlinna, Finland) with the following settings:

Inspiratory flow rate	0.5 l/s
Starting volume	50 ml
Duration of nebulization	0.8 s
Output	10.3 µl per breath

By administering the incrementally increasing concentrations of lysine-aspirin and by varying the number of breaths from the nebulizer, geometric (exponential) progression in the cumulative doses of lysine-aspirin is created (Table 2, Fig. 2).

*Challenge protocol.* Forced expiratory volume in 1 s is measured and the baseline value is chosen as the best of three consecutive efforts. The challenge commences if the baseline FEV<sub>1</sub> is at least 70% of the predicted value. The test begins with the inhalation of seven breaths of diluent (saline). Forced expiratory volume in 1 s is measured at 10 and 20 min after inhalation. Provided that postsaline FEV<sub>1</sub> does not decrease > 10% the challenge with lysine-aspirin is commenced. The postsaline FEV<sub>1</sub> obtained at 20 min is used as 'postsaline baseline' value.

Table 2. Solutions and doses of lysine-aspirin used in the inhalation aspirin challenge

Concentration of lysine-aspirin (M)	Number of inhalations	Inhaled dose of aspirin (mg)	Cumulative dose of aspirin (mg)
0.1	1	0.18	0.18
0.1	2	0.36	0.54
0.1	5	0.90	1.44
0.1	13	2.34	3.78
1	4	7.20	10.98
1	9	16.2	27.18
2	11	39.60	66.78
2	32	115.20	181.98

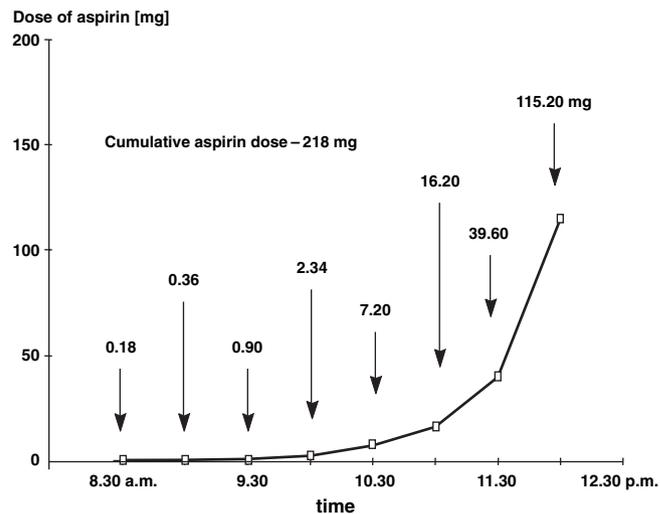


Figure 2. Inhalation aspirin challenge flowchart.

The consecutive doses of lysine-aspirin are inhaled every 30 min by increasing the concentration of lysine-aspirin and by changing the number of breaths (as presented in Table 2). Forced expiratory volume in 1 s is measured at 10, 20 and 30 min after each dose. The provocation is stopped if a fall in FEV<sub>1</sub>  $\geq$ 20% as compared with postsaline baseline value in FEV<sub>1</sub> occurs (a positive reaction), or the maximum cumulative dose of lysine-aspirin is reached without any adverse symptoms (a negative reaction).

If a decrease in FEV<sub>1</sub> at 30 min after inhalation is between 15% and 20% it is recommended to wait another 10 min before administering the next dose and repeat the FEV<sub>1</sub> measurement. If FEV<sub>1</sub> decreases by  $\geq$ 20% from the postsaline baseline the challenge is stopped. If the drop remains between 15% and 20% the supervising physician has to make a decision as to whether or not the next dose should be administered. If the patient has moderate to severe asthma or the dose-response curve in relation to lysine-aspirin is steep it is recommended to repeat the previous dose, rather than administering the next dose.

In the case of a positive reaction a dose-response curve is constructed to calculate the PD<sub>20</sub>. The lowest FEV<sub>1</sub> out of three measurements (at 10, 20 and 30 min) obtained after each dose is plotted against the log<sub>10</sub> cumulated dose of aspirin and the PD<sub>20</sub> is calculated by linear extrapolation.

#### Patient supervision after oral and/or inhalation challenge

In the case of a positive reaction the symptoms are relieved by the inhalation of 2–4 puffs of short-acting  $\beta_2$ -agonist or by nebulization (e.g. 2.5–5.0 mg of salbutamol) until the FEV<sub>1</sub> returns to within 90% of the baseline value. If more severe reactions are observed oral or i.v. corticosteroids (40 mg of prednisolone or equivalent) are administered. Anaphylactic reactions require immediate intramuscular injections of epinephrine – see respective guidelines (33).

Ideally, after a positive oral aspirin challenge the patient should be hospitalized until the following morning and FEV<sub>1</sub> is then recorded. The patient should remain under observation for at least 1 h after the completion of an aspirin inhalation challenge and the FEV<sub>1</sub> value should have returned to within 10% of the prechallenge baseline before discharge from the hospital. The patient should be provided with a peak expiratory flow (PEF) meter and record the PEF values before leaving the hospital and every 2–3 h until late evening. In the case of any respiratory symptoms and a 20% decline in PEF value, the patient should take short acting  $\beta_2$ -mimetic and contact the physician responsible for the aspirin challenge procedure.

#### Single-blind, placebo-controlled nasal aspirin challenge (in patients suspected of suffering from AIA/R/nasal polyposis)

Nasal aspirin challenge may be considered in patients with severe asthma in whom oral or bronchial aspirin

challenges are contraindicated. This type of provocation may be supervised in a hospital outpatient clinic. Before the challenge all patients should undergo rhinological examination with anterior rhinoscopy to evaluate the presence of nasal polyps. Any pathology of the nasal cavity, such as septal perforation or massive nasal polyposis which could influence the outcome of nasal aspirin challenge is a contraindication to the nasal challenge procedure. A stabilization period of at least 30 min should precede the nasal aspirin challenge to exclude the influence of environmental factors on nasal hypersensitivity.

Drug withdrawal before nasal aspirin challenge:

Nasal corticosteroids	7 days (or the lowest possible dose kept stable through the aspirin challenge)
Oral corticosteroids	7 days (or the lowest possible dose kept stable thorough the aspirin challenge)
Short-acting antihistamines	3 days
Nasal $\alpha$ -mimetics	24 h
Oral $\alpha$ -mimetics	24 h
Local cromones	24 h
Leukotriene modifiers	At least 1 week

At least one of the following methods of challenge assessment should be included in the records:

#### 1 Clinical symptoms:

- Rhinorrhoea, nasal congestion, sneezing, itching of the nose, palate or throat, ocular injection or, rarely, skin flushing or dyspnoea.
- The intensity of symptoms, which are assessed every 10 min, can be quantified with a 10 cm visual analogue scale; the number of sneezes could also be counted.

#### 2 Acoustic rhinometry:

- The most useful parameter evaluated by acoustic rhinometry is the total nasal volume at 12 cm (the volume of the nasal cavity is measured from the distal extreme of the nosepiece to 12 cm from the rear).
- The measurements are taken every 10 min, three times in apnea after a nonforced expiration and discarded when the coefficient of variation is over 5%.

#### 3 Active anterior rhinomanometry:

- Both left and right nasal inspiratory flows are assessed by active anterior rhinomanometry. The readings are taken at the same time points as for acoustic rhinometry.
- Active anterior rhinomanometry is not carried out in subjects with nasal inspiratory flow below 250 ml/s at baseline, or those experiencing a fall exceeding 20% in nasal inspiratory flow following saline instillation (see below).

#### 4 Peak nasal inspiratory flow (PNIF) – the Youlten PNIFmeter could be used:

- The readings are taken at the same time points as for acoustic rhinometry.

During nasal challenges peak expiratory flow rate (PEFR) and/or FEV<sub>1</sub> measurement are taken at the same time points to monitor the lower respiratory tract. Lysine-aspirin solution preparation (see Single-blind, placebo-controlled bronchial aspirin challenge). Alternatively Aspegic (Synthelabo; 500 mg sachets) can be used.

Protocol of nasal aspirin challenge

At baseline nasal symptoms, inspiratory flows and nasal volumes are recorded during the first 30 min at 10-min intervals. Then the nasal challenge with 0.9% NaCl (80 µl) instilled into each nostril via an Eppendorf pipette is carried out for assessment of nonspecific nasal hyper-reactivity. Nasal symptoms, inspiratory flow and nasal volumes are measured over the following 30 min at 10-min intervals. If a change over 20% in the recorded values occurs then the upper airway is hyperreactive and further challenge could not take place. Finally L-ASA 80 µl (total aspirin dose – 16 mg) is instilled (using an Eppendorf pipette) into each nostril with the patient's head tilted back for 1 min.

Following L-ASA (80 µl) administration nasal symptoms, inspiratory flow and nasal volumes are measured in the following 2 h at 10-min intervals. In patients who develop clinical symptoms by the end of 2 h of observation, nasal symptoms, inspiratory flow and nasal volumes are measured throughout the following hour (third hour following L-ASA administration) at 10-min intervals.

A positive reaction to nasal aspirin challenge is defined as the appearance of nasal symptoms such as rhinorrhoea, nasal congestion, sneezing and 25% decrease of total nasal flow value at 12 cm, as compared with baseline measured by acoustic rhinometry or 40% bilateral drop of inspiratory nasal flow, as compared with the baseline value assessed by rhinomanometry or PNIFmeter. Nasal α-mimetics (e.g. topical oxymetazoline) are used to treat nasal obstruction following nasal aspirin challenge. In the case of severe nasal adverse reactions oral corticosteroids may have to be administered. A negative nasal challenge should be followed by oral challenge to rule out aspirin sensitivity beyond reasonable doubt.

**Single-blind, placebo-controlled oral aspirin challenge test in patients suspected of aspirin-induced urticaria**

Ideally subjects should be challenged when their urticaria is in remission, e.g. at least 1–2 weeks before the test patients should be without any skin eruptions. This, however, might be hard to achieve in some patients. Thus, the patients could continue their regular medications, including oral corticosteroids in doses not exceeding 10 mg of prednisone per day. Other medications

should be withdrawn in line with the guidelines (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin). The oral challenge procedure is identical as for the diagnosis of AIA (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin). However, there are some special considerations for oral aspirin challenge in patients with AIU.

- 1 Careful monitoring of skin eruptions is necessary throughout the challenge procedure and for at least 6 h after the last dose of aspirin or placebo.
- 2 The challenge procedure is interrupted if cutaneous reactions appear or when other symptoms of aspirin hypersensitivity develop (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin).
- 3 The assessment of severity of the skin eruptions is assessed by the Urticaria Severity Index (sum of score 0–6) (Table 3). Wheals and pruritus are assessed on the scale from 0 to 6, with 0 indicating no eruptions and pruritus and 6 indicating intense or large confluent areas of wheals and severe pruritus. Urticaria Severity Index determinations are carried out at the time of the first appearance of skin lesions and 2, 4, 6 h later. If no skin symptoms occur the patients should still be observed for 4–6 h.
- 4 Cutaneous adverse symptoms are relieved by the administration of antihistaminics and/or oral or intravenous corticosteroids. If incipient anaphylaxis is suspected (e.g. angioedema, generalized urticaria) epinephrine should be used according to guidelines (33).
- 5 Pulmonary function tests should be measured as a certain proportion of patients with AIU are likely to develop bronchial adverse reactions.
- 6 Other possible adverse symptoms of aspirin hypersensitivity should also be duly noted (see Oral single-blind, placebo-controlled diagnostic challenge tests with aspirin).

Protocol of oral aspirin challenge for the aspirin-induced urticaria patients

The single-blind, placebo-controlled oral challenge test with aspirin is carried out during two consecutive days. On the first day four capsules of placebo are administered

Table 3. Modified Urticaria Severity Index (34)

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/the period of challenge)	Mild
2	Moderate (21–50 wheals/the period of challenge)	Moderate
3	Intense (>50 wheals/the period of challenge or large confluent areas of wheals)	Intense

The sum of score is 0–6.

Table 4. Aspirin challenge for diagnosis of aspirin-induced urticaria

Consecutive doses of aspirin (mg)	Cumulative doses of aspirin (mg)
71*	71
117	188
312	500
500	1000

\*Optionally the challenge procedure may commence with smaller doses (10, 27, 44 mg) if severe skin sensitivity is predicted, in line with the flowchart for diagnosis of aspirin-induced asthma (see paragraph I).

every 1.5–2 h. On the second day the patients are challenged with exponentially increasing doses of 71, 117, 312 and 500 mg of aspirin, at 1.5–2 h intervals, up to a cumulative dose of 1000 mg of aspirin (Table 4). Placebo and aspirin are identical in appearance. The challenge procedure with aspirin is interrupted if skin reaction occurs or if the maximum cumulative dose of

aspirin is reached. Forces expiratory volume in 1 s and extrabronchial symptoms are recorded at baseline, before the challenge tests, and then every 30 min until 6 h after the last dose of aspirin.

In summary, we recommend:

**1 Oral aspirin challenge:**

- For diagnosis of AIA, AIA/R and AIU in experienced medical centres.
- For diagnosis of AIA after negative inhalation and/or nasal challenge if clinical suspicion remains.

**2 Nasal challenge:**

- For diagnosis of AIR.
- For diagnosis of AIA or AIA/R in subjects that cannot undergo oral or inhalation challenge because of low lung function or brittle/severe asthma.

**3 Inhalation challenge:**

- For diagnosis of AIA or AIA/R.

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