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POSITION PAPER

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EAACI Position paper on the standardization of nasal allergen challenges

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Abstract

Nasal allergen challenge (NAC) is an important tool to diagnose allergic rhinitis. In daily clinical routine, experimentally, or when measuring therapeutic success clinically, nasal allergen challenge is fundamental. It is further one of the key diagnostic tools when initiating specific allergen immunotherapy. So far, national recommendations offered guidance on its execution; however, international divergence left many questions unanswered. These differences in the literature caused EAACI to initiate a task force to answer unmet needs and find a consensus in executing nasal allergen challenge. On the basis of a systematic review containing nasal allergen challenges of the past years, task force members reviewed evidence, discussed open issues, and studied variations of several subjective and objective assessment parameters to propose a standardized way of a nasal allergen challenge procedure in clinical practice. Besides an update on indications, contraindications, and preparations for the test procedure, main recommendations are a bilaterally challenge with standardized allergens, with a spray device offering 0.1 mL per nostril. A systematic catalogue for positivity criteria is given for the variety of established subjective and objective assessment methods as well as a schedule for the challenge procedure. The task force recommends a unified protocol for NAC for daily clinical practice, aiming at eliminating the previous difficulty of comparing NAC results due to unmet needs.

KEYWORDS
allergic rhinitis, diagnostic tools, nasal allergen challenge, nasal provocation test

1 | INTRODUCTION

Allergic rhinitis is one of the most debilitating diseases of our times: It is estimated that 500 million people worldwide (20% of the population) are affected by symptoms of allergic rhinitis, leading to severe health impairment and increased medical costs, as well as decreased work force and man power due to sick leave/down times. Furthermore, frequent comorbidities such as asthma, eczema, food allergies, rhinosinusitis, and other reactions significantly contribute to the burden of this disease.

A correct diagnosis is essential for adequate therapy. A thorough history, physical examination, and allergy tests (including skin prick test and specific serum IgE) can lead the way. However, allergen challenge tests are a safe and straightforward technique and recommended in order to identify phenotypes of the disease or to identify those allergens against which specific allergen immunotherapy is a promising option.[1]

1.1 | Objective

After one decade of using nasal allergen challenge (NAC) on the basis of existing guidelines and publications,[2,3] a unified and internationally consented version is presented here. There are some discrepancies and unmet needs in existing important papers. This leads to difficulties when comparing results between studies using NAC.[4,5] Unmet needs on unifying methodologies are, for example, allergen dose and quality, allergen application technique, the need of a titration process, provocation of either 1 or 2 nostrils, or the best methods to assess subjective and objective outcomes.[4,5]

Recently published position papers have mentioned NAC[6,7] but lack a unified guideline how to utilize it in daily practice. Therefore, the Ear, Nose and Throat section of the European Academy of Allergy and Clinical Immunology (EAACI) originated a Task Force (TF) on the "Standardization on Nasal Allergen Challenges" in 2016.

The aim of this TF was to

1. collect evidence on open methodologic questions,
2. evaluate and critically discuss new technical improvements and scientific findings that were made during the last 15 years and
3. recommend a consensus position from a panel of experts in order to harmonize NAC throughout Europe and beyond.

We aimed at providing a guideline for the daily use of NAC in common clinical practice.

1.2 | Definition

Nasal allergen challenge (NAC) reproduces an allergic reaction of the nose under standardized and controlled conditions.[8] This simple, safe, and cheap technique has been internationally established in many countries as a standard procedure to diagnose allergic rhinitis.[9,10]

Applying an allergen to the nasal mucosa provokes an immediate type 1 immune reaction and evokes cardinal symptoms of rhinitis[11] such as sneezing, itching, nasal airway obstruction, and nasal secretion. Commonly associated are ocular symptoms, while systemic reactions and exanthema are rare. The clinical changes can be assessed subjectively or objectively by either symptom scores or different objective methods of measuring nasal patency. This position paper is meant to serve as a practical guide in clinical settings.

2 | METHODS

A systematic review of the literature was performed in PubMed and Web of Science databases, using the following keywords: (Nasal Provocation Test [major]) OR (Nasal Provocation Testing) OR (Nasal Allergen Challenge). The search was limited to trials in human species and publication dates from 2004 to 2016. The search was performed in German and English language, and 786 studies were retrieved.

Manual explorations of the reference lists of these 786 studies were performed and relevant studies identified by 3 independent reviewers. Studies were considered for evaluation in this position paper if they included a nasal application of a specific standardized allergen in human subjects. A clinical nasal patency test including symptom scores or objective measurement had to be part of the outcome parameter.

In the end, 173 papers meeting all criteria were selected (Figure 1, Literature research). TF members reviewed the selected studies with special attention to existing guidelines.[3,12,13] They had the possibility to suggest also other publications than the studies previously identified, in case these were likewise matching the criteria listed above. The methods and results of those papers were summarized in Table S1 (body of evidence).

During 5 meetings and international conferences, task force members met to elaborate this position paper and to find answers for unmet needs. Online discussions throughout this course completed the opinion finding process. Some of the recommendations were based on consensus-driven proposals from the TF working group.

This position paper consists of recommendations elaborated by the TF participants. EAACI is solely responsible for this publication, which does not represent an official document of any governmental agency.

3 | RESULTS

3.1 | Indications, contraindications, preparations for nasal allergen challenge

3.1.1 | Indications and contraindications

Nasal allergen challenge is a means of clinically reproducing a disease. Furthermore, it is often used as an important outcome parameter in therapeutic trials.[13] The diagnosis of allergic rhinitis with consecutive immunotherapy is based upon patient's history, physical examination, skin prick testing, and specific serum IgE level measurements. Clinical implications of biomarker measurements ("the precision medicine approach") in the concept of disease endotypes are an improved knowledge of the pathogenesis of the underlying disease among others.[14] The serum biomarkers should ideally be supplemented by nasal function measurements, such as nasal flow measurement to confirm nasal obstruction and nasal allergen provocation to confirm the clinical relevance of allergens.[14] There are cases where the history is highly suggestive of allergies; however, either symptoms or history does not match the results of skin or blood testing, or skin prick testing cannot be evaluated due to urticaria, atopic dermatitis, or certain medication.[15]

Respecting guidelines and review articles,[3,4,12-14] an overview of main clinical indications and contraindications is given in Tables 1 and 2.

Certain systemic or local therapies can interfere with the response to NAC and should be considered when planning NAC. Any medication with elevated risk of intolerance, allergic reaction, or drug interference should be discontinued for a given washout period (Level of evidence V, grade of recommendation D).[13]

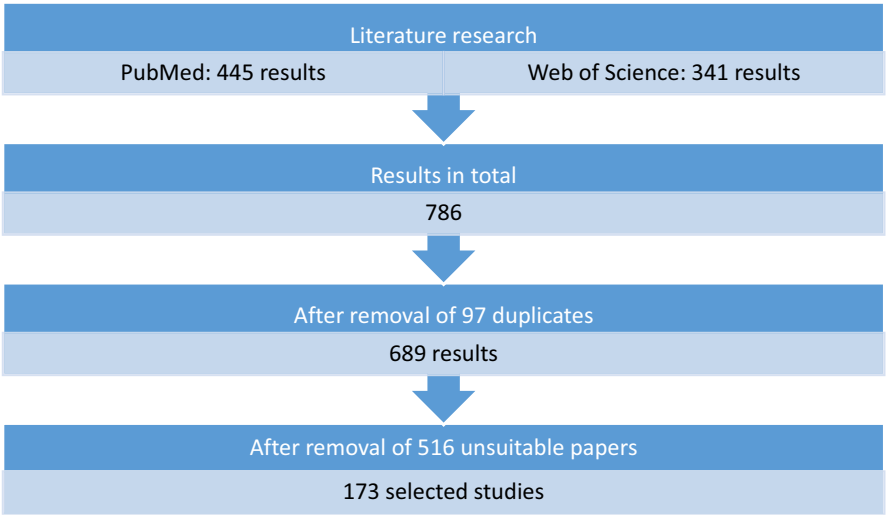

FIGURE 1 Literature research for the body of evidence

TABLE 1 Levels of evidence and grades of recommendation

Level of evidence	
Level I	Systematic reviews, meta-analysis, randomized controlled trials
Level II	Two groups, nonrandomized studies (e.g., cohort, case-control)
Level III	One-group nonrandomized (e.g., before and after, pretest, and post-test)
Level IV	Descriptive studies that include analysis of outcomes (single-subject design, case-series)
Level V	Case reports and expert opinion that include narrative literature, reviews, and consensus statements
Grades of recommendation	
Grade A	Consistent level I studies
Grade B	Consistent level II or III studies or extrapolations from level I studies
Grade C	Level IV studies or extrapolations from level II or III studies
Grade D	Level V evidence or troublingly inconsistent or inconclusive studies at any level

TABLE 2 Indications and contraindications for NAC

Indications

- Diagnosis of:
  - Persisting allergic rhinitis[16,17]
  - Intermittent allergic rhinitis[17,18]
  - Local allergic rhinitis[19-26]
  - Occupational rhinitis[27-30]
- Correlation with extranasal symptoms[31,32]
- Differential diagnosis of ocular symptoms[33]
- Further Evidence diagnosing food allergy[34,35]
- To design allergen composition and to monitor clinical efficacy of immunotherapy[36-39]

Contraindications

Absolute contraindications:

- Previous anaphylactic reaction to the allergen
- During an acute inflammation of the nose or paranasal sinuses[13,40,41]
- Severe comorbidities (e.g., cardiopulmonary diseases, impairment of lung capacity[3,40])
- Extremely high grade of sensitization (e.g., severe and uncontrolled bronchial asthma or chronic obstructive pulmonary disease[3,40])
- Other severe systemic diseases (e.g., malignant tumors, autoimmune diseases[42])
- Systemic immunotherapy
- During pregnancy[3,40]

Relative contraindications:

- Infants under the age of 5[43,44]
- Unstandardized allergen extracts due to a lack of comparability and reproducibility

Temporary contraindications:

- Acute allergic reactions in other organs[12]
- Vaccination (wait 1 wk)[12]
- Acute viral or bacterial infection (wait 4 wk)[45]
- Surgery of the nose or paranasal sinuses (postpone for 6-8 wk)[40]
- Recent use of alcohol or tobacco for 24-48 h before NAC[3]

3.1.2 | Examination

A thorough inspection of the external nose and face follows the history, possibly revealing clues for allergic constitution (e.g., allergic crease, Dennie Morgan lines and shiners below the eyes, or an allergic crease on the nasal dorsum). This is followed by anterior rhinoscopy to inspect the anterior parts of the nasal cavities, for evaluating the presence of nasal discharge or mucosal swelling, crusting, septal perforations, or polyps. Anterior rhinoscopy is limited in its evaluation of the entire nasal cavity and therefore should be followed by nasal endoscopy offering the advantage of a global evaluation of the endonasal cavity with all 3 meatus, the ostia of the paranasal sinuses, and the nasopharynx. It is also an important tool to exclude rhinosinusitis. Lastly, variations exist between different examiners' observations and interpretations.[46] Rigid endoscopy is quicker and more patient friendly than flexible endoscopy (Level of evidence III, grade of recommendation B[41]).

Several nasal pathologies can affect nasal patency. This may lead to technical difficulties in assessing the outcome of an allergen challenge. Therefore, it is very important to assess baseline conditions of nasal function before provocation. The pathologies affecting nasal patency include the following:

- Choanal atresia[12]
- Chronic rhinosinusitis with nasal polyps[47]
- Septal perforation and severe septal deviation[3,12]
- Atrophic rhinitis
- Adenoids obstructing nasal ventilation

3.1.3 | Test day/seasonality

Besides patient's history, the skin prick test or serum-specific IgE values should be completed and their results present in order to evaluate specific sensitizations to ensure the right indication and the correct allergen to be tested.

Several studies have shown that previous exposure to allergens can affect nasal patency.[48-52] Using seasonal allergens, NAC should be performed a minimum of 4 weeks after the pollen season (Level of evidence II, grade of recommendation B[52]). Provocation with perennial allergens such as house dust mites, molds, or animal dander can only be tested perennially, if the patient has mild symptoms that do not interfere with the test result.[3]

Allergen challenge should preferably be performed in the morning. Patients should avoid any irritant effects (e.g., tobacco smoke, spicy food, or coffee[3,53]) to minimize false results. In addition, physical or mental stress may have an influence in the test performance (Level of evidence V, grade of recommendation D[3]).

3.1.4 | Room conditions

Allergen challenges cannot fully replace real-life studies. It is thus necessary to provide a controlled test environment to achieve reproducible results. Thus, environmental variations should be avoided,[6]

and NAC should be performed under standardized room conditions, including previous exposition, acclimation time, room temperature, and humidity.[54]

For a proper implementation, patients should be well adapted to the climatic conditions of the examination room.[54] While conditions are best controlled using allergen exposure chambers, room conditions in NAC with spray devices need standardization.[54]

The room must not be contaminated by other substances (methacholine, test puffs of the allergen spray, etc.). Mandatory test puffs (if using a spray) must be conducted in another room, under a hood, or against a gauze/cotton pad for better test accuracy and patient safety.[12] In addition, various emotional stimuli may influence nasal mucosal swelling, such as simple communication with the patient or a person entering the room. Therefore, such stimuli should be avoided,[55] and a calm and quiet atmosphere should be assured. We recommend a standardized room acclimation time of 15 minutes before baseline evaluation (Level of evidence II, grade of recommendation B[12,56]). A room temperature of 20 ± 1.5°C should be assured with a recommended humidity of 40%-60% (Level of evidence V, grade of recommendation D[3]).

If performed properly, multiple challenges can be executed any time in the same challenge room (Level of evidence V, grade of recommendation D).

3.1.5 | Personnel

Personnel should have adequate knowledge of physiological assessments of nasal patency and access to therapeutic measures in case of a nasal or systemic reaction.[3] Physicians and trained nurses under supervision or with direct access to a physician trained in emergency management can perform the test. The staff performing NAC underlie specific regulations of each country, so that every physician indicating this test has to take the responsibility of delegating the testing procedure or not (Level of evidence V, grade of recommendation D[3]).

3.1.6 | Emergency medication

Although it has never been reported, an anaphylactic reaction can occur after nasal allergen challenge. Therefore, patients should sign an informed, written consent document before undergoing the test.[3] A prerequisite for performing NAC is to have an emergency kit at hand. Equipment, drugs, and fluids should always be available while performing allergy procedures.[57] All medical staff involved in allergy procedures should be trained in the recognition and management of allergic emergencies, an emergency staff (intensive care unit) should be available within 30 minutes.[44] It is advisable to have access to a spirometer to monitor lung function and a flow oxygen unit in the unlikely event of anaphylaxis and bronchospasm. Besides antihistamines (oral/i.m.), corticosteroids (oral/i.m.), short acting beta-2 (β-2) agonists (inhaled), and adrenaline (i.m./autoinjector), nasal decongestants are useful to treat symptoms of an intense positive allergic reaction (Level of evidence V, grade of recommendation D[3]). Algorithms for the management of allergic emergencies can be found in anaphylaxis guidelines.[58,59]

3.2 | Allergens and challenge technique

3.2.1 | Allergens

Allergens are sold in ready-to-use, standardized solutions and should be used following the manufacturers' guidelines. Some allergens are also available as a freeze-dried lyophilisate and should be suspended in an aqueous solution immediately before use, as potencies of dilutions decrease rapidly.[60] Test solutions should be isotonic and pH neutral.[12]

Expiration dates of lyophilisates, solutions and control solutions should be checked before application. The specific summary of product characteristics (SPC) should be adhered to for the specific products used. After being stored in the refrigerator at 4°C, the allergen solution should be brought to room temperature to avoid mucosal irritation.

There are different manufacturers of allergen provocation solutions on the market. Numerous concentration units (SQ-U/mL, SBU/mL, AU/mL, HEP/mL, or w/v %) unfortunately make it impossible to compare the allergen concentration of the different allergen solutions. Besides, TF members determined a decreasing availability of nasal challenge allergen products in European countries due to registration barriers.

Literature research has shown that SQ-U/mL is the quota/unit used by most of the studies (see Table S1). However, the TF members do not recommend one of the manufacturers units but support the usage of SI units, for example, in μg/mL major allergen content. We refer to the Standard Summary of Medicinal Product Characteristics (SMPCs) of the manufacturers for the clinical use of allergens in NAC. This may not be the case for scientific evaluations.

Allergen titration should be limited to research settings, therapy control (testing the response to certain treatments, if continuation of therapy needs to be decided), dose finding processes (to determine the sensitivity threshold of each allergen in research settings),[61] or patients with extremely high grades of sensitization, in whom the standardized concentration might evoke anaphylaxis and asthma attacks.[35]

3.2.2 | Application of allergens

Several methods for allergen application have been used in the past. Pump-aerosol spray has been claimed to be the easiest and most reliable device available.[10] Dispensing an exact amount of solution, usually 50 μL/puff, it can be applied without irritation of the mucosa.[4,7] The Task Force recommends an allergen application by spray bottles with a 50 μL/puff nozzle. There is a risk of depositing the allergen in the pharynx, which may cause irritation of the lower airways. In daily practice, this risk can easily be avoided by giving precise instructions to the patient during the challenge procedure.

3.2.3 | Application technique for spray devices

We concur with the predominant opinion to bilaterally challenge and assess nasal patency (Level of evidence V, grade of recommendation D[3]).

Fifty-nine of the 173 investigated studies used a defined amount of 0.1 mL allergen solution (see Table S1—body of evidence). Implementing a test puff ensures that the medication chamber of the spray device contains the full amount of solution and dispenses the proper amount of aerosol. The advantage of a test puff is also the higher reproducibility of studies.

Based on the device used, the allergen should be applied by giving 2 puffs (of 0.05 mL per puff) per nostril, one in the inferior meatus and one on the direction of the middle turbinate. This technique aims to cover the mucosa of the inferior and middle portion of the nasal mucosa with the test allergen. It should be avoided to spray toward the nasal septum to prevent mechanical irritation.[4,62-64] The precise instructions are to take a deep breath before, hold breath during, and exhale profoundly after application of the allergen.[4,12] This technique prevents aerosol penetration of the lower respiratory tract via the nasopharynx, which is one possible adverse event of NAC.

3.3 | Subjective/semiquantitative measurement

In a systematic review, André et al concluded that comparing subjective and objective assessments of the nasal airways show every possible combination of strong, weak, or even inverse correlations. In addition, objective measurements cannot predict the subjective feeling reported by patients.[65]

Subjective and objective parameters assess different aspects of nasal obstruction. Therefore, nasal obstruction should be evaluated in combination with at least one subjective and one objective parameter[66-68] and assessing clinical symptoms should be set as the most relevant outcome parameter in allergen challenges.[3,9,12,69] Other semiquantitative methods such as counting sneezes or weighing nasal secretions are valid, yet seem less practicable and reliable.

3.3.1 | Symptom scores

There are different semiquantitative, subjective measures to evaluate nasal symptoms, for example, reporting organ-related symptoms on a Likert scale (0 = none, 1 = mild, 2 = moderate, or 3 = severe)[70] or visual analog scales (VAS)[71,72] with the latter reporting the severity of symptoms on a 0- to 100-mm horizontal scale (mild: 0-30 mm; moderate: 31-70 mm; and severe: 71-100 mm).[10]

Total Nasal Symptom Score (TNSS) is a 12-point scale derived by summing scores for 4 symptoms (rhinorrhea, nasal obstruction, sneezing, and nasal itching). Assessed in a Likert scale, the maximum TNSS scores are 12 points.

The task force members concurred that the ideal subjective scale would contain the following 5 symptoms: sneezing, nasal pruritus, rhinorrhea, nasal obstruction, and ocular symptoms. These key symptoms are also included in Linder and Lebel scores.[73-75] According to the ARIA guidelines, the use of VAS in reporting congestion, sneezing, itching, and rhinorrhea by patients with a vertical line on a scale between 0 and 100 mm is a clear and easy-to-use method for measuring severity of allergic rhinitis.[76]

Demoly et al showed in nearly 1000 patients that a simple VAS self-assessment of therapeutic improvement of allergic rhinitis symptoms is statistically related to RQLQ and TSS6 and much easier to assess (Level of evidence IV, grade of recommendation D[72]). Del Cuvillo et al[77] showed in 3572 patients that a self-assessment of the ARIA symptoms (allergic rhinitis and its impact on asthma) by VAS can differentiate allergic rhinitis easily and reliably into the 3 severities mild, moderate, and severe. VAS measures have been recently validated for measuring the severity of allergic rhinitis and also correlated well with pharmacomedical treatment.[71] They are also frequently reported as being complementary to other measurements.[6,66,71,78] However, there is a high degree of heterogeneity on which (organ-specific) symptoms to assess by VAS (see Table S1).

A standardized visual analog Scale (VAS) (Level of evidence I, grade of recommendation A[72]) as suggested by ARIA was the main opinion of TF members to be used as subjective measure. This scale is a self-assessment of patients' symptoms and should be filled in by patients, assisted by the investigator evaluating the symptoms sneezing, rhinorrhea, or ocular symptoms together.

3.4 | Objective assessment of nasal patency

Various technical methods to assess and objectify nasal airflow and ventilation have been developed. Many are laborious or costly and often do not represent patients' subjective symptoms. The nasal airway resistance is related to the 4th power of the cross-sectional area of the nose, so that minimal changes of the diameter cause big changes in the resistance (law of Hagen-Poiseuille). Neither the human eye can estimate the degree of impairment of the nasal patency, nor are measurements of the diameter of the nose sufficiently related to the nasal airway resistance.[79]

Nasal patency can be objectively assessed by the following methods:

- Peak nasal inspiratory flow (PNIF) is the easiest and cheapest method to measure nasal airflow, but it is strongly dependent on patients' collaboration and lung function. Thus intermeasurement variations can be significant and a measurement depicts only a momentary inspiration.[9,80]
- Acoustic rhinometry (AcRh) is quick and easy to perform, without the need of patient collaboration. It was standardized in 2005 by the Standardization Committee on Objective Assessment of the Nasal Airway of the European Rhinology Society.[8,81]
- Active anterior rhinomanometry (AAR) is a sensitive, highly specific method and currently accepted as international standard method for objective nasal patency measurements.[82]
- 4-phase-rhinomanometry (4PR) is reported to be the most reliable technical method to assess nasal ventilation and patency, as well as the nasal valve region.[83]

The consensus of this TF was to accept all above-mentioned, objective, and established methods and concurs that one criterion

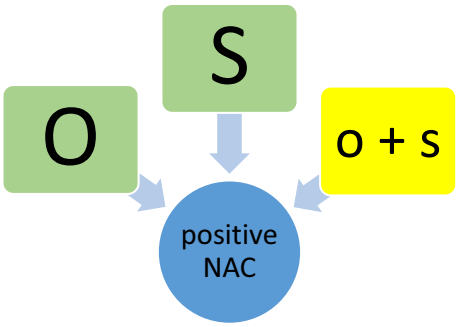

FIGURE 2 Positive NAC results (Objective assessment is strongly positive [O]; Objective assessment is moderately positive [o]; Subjective assessment is strongly positive [S]; Subjective assessment is moderately positive [s])

suffices to diagnose a positive NAC, if it is strongly positive. NAC results can be seen as positive in the following way (Figure 2):

- Strong increase in objective measurement = O or
- Strong increase in subjective symptoms = S or
- moderate increase in two criteria (objective and subjective measurement) = o + s

3.4.1 | Outcome interpretation

When interpreting the reaction after nasal allergen challenge, there are various valid measures to be used, which are summarized in Table 3.

3.5 | Challenge procedure and timing

The actual challenge procedure can be divided into 3 steps of measurements, containing a baseline measurement, a control challenge, and the allergen challenge, subjectively and objectively assessing nasal ventilation at each step.

In the first (baseline) measurement, nasal ventilation should be assessed before any substance has been applied to compare results of the control challenge and allergen challenge with the initial value.

As some allergen solutions contain preservatives that may react with the nasal mucosa, it is then necessary to perform a control challenge with the same diluent that is used to prepare the allergen solutions. Such hyper-reactivity may occur in all types of rhinitis.[84] The German and Spanish guidelines[3,12] recommend application of the control agent at the wider side of the nose with a single time point of objective and subjective evaluation. However, the task force recommends bilateral challenge of control and allergen substances.

If the control solution causes <50% of the positivity criteria, one can proceed with the application of the test allergen. If the reaction under the control agent is ≥50% of a positive reaction, we recommend that the test is halted and a new test is scheduled after a few days (Level of evidence V, grade of recommendation D[1]).

To have optimal comparability of the control challenge with the allergen reaction, timing of assessment should also be unified. In previous recommendations and papers, 10 or 15 minutes has been used.[4,12] Control challenge scores should be evaluated 10 minutes after applying the control solution to measure clinical symptoms and changes in objective measurements of nasal patency. If no significant changes occur, the actual allergen provocation can be performed. Afterwards, symptoms and changes in objective measurements of nasal patency should be recorded 10 minutes after applying the allergen. Symptom scores are to be filled out once, while objective outcome is to be measured with 3 measurements in a row in order to eliminate technical problems. We agreed that a single measurement is sufficient if the test outcome is positive. In case of a negative result, measurement can be repeated after another 10 minutes (Level of evidence IV, grade of recommendation D) (Figure 3).

3.5.1 | Follow-up

The patient should be kept under observation for at least half an hour until the reaction ceases.[44] Patients should have access to

TABLE 3 Recommendations for evaluating NAC as positive

Method	Clearly positive (S; O)	Moderately positive (s; o)
Subjective measures		
Visual analog scale (VAS)	Symptoms ≥55 mm	Symptoms ≥23 mm
Lebel score	Increase of ≥5 points	Increase of ≥3 points
Linder score	Increase of ≥5 points	Increase of ≥3 points
Total nasal symptom score (TNSS)	Increase of ≥5 points	Increase of ≥3 points
Objective measures		
Peak nasal inspiratory flow (PNIF)	Flow decrease of ≥40%	Flow decrease of ≥20%
Acoustic rhinometry (AcRh)	CSA-2 decrease of ≥40%	decrease in sum of 2-6 cm^3 ≥27% bilaterally
Active Anterior rhinomanometry (AAR)	Flow decrease of ≥40% at 150 Pa	Flow decrease in ≥20% at 150 Pa
4-phase-rhinomanometry (4PR)	≥40% increase in logarithmic (lg) effective resistance	≥20% increase in lg effective resistance

topical nasal decongestants and topical or systemic antihistamines. Systemic reactions should be treated according to the guidelines. Patients should be advised that a delayed reaction up to 12 hours can occur. Results of a late response are difficult to be included in clinical assessment routine of NAC and can be disregarded (Level of evidence II, grade of recommendation B).[85,86]

3.6 | Potential sources of error

3.6.1 | False-positive results

Possible reasons for false-positive test result are as follows:

- Changes in the nasal cycle
- Drugs interfering with the test results
- False temperature of substances
- Recent allergen exposure, contamination of the examination room or allergen
- Lack of adaptation to room climate
- Lack of control of nasal hyper-reactivity
- Lack of control of irritant reactions due to impurities or preservatives of allergens (e.g., glycerin)
- Irritating pH (<5 or >8) or hypo-/hyperosmolality in individually prepared extracts[40]
- Faulty delivery of test solution

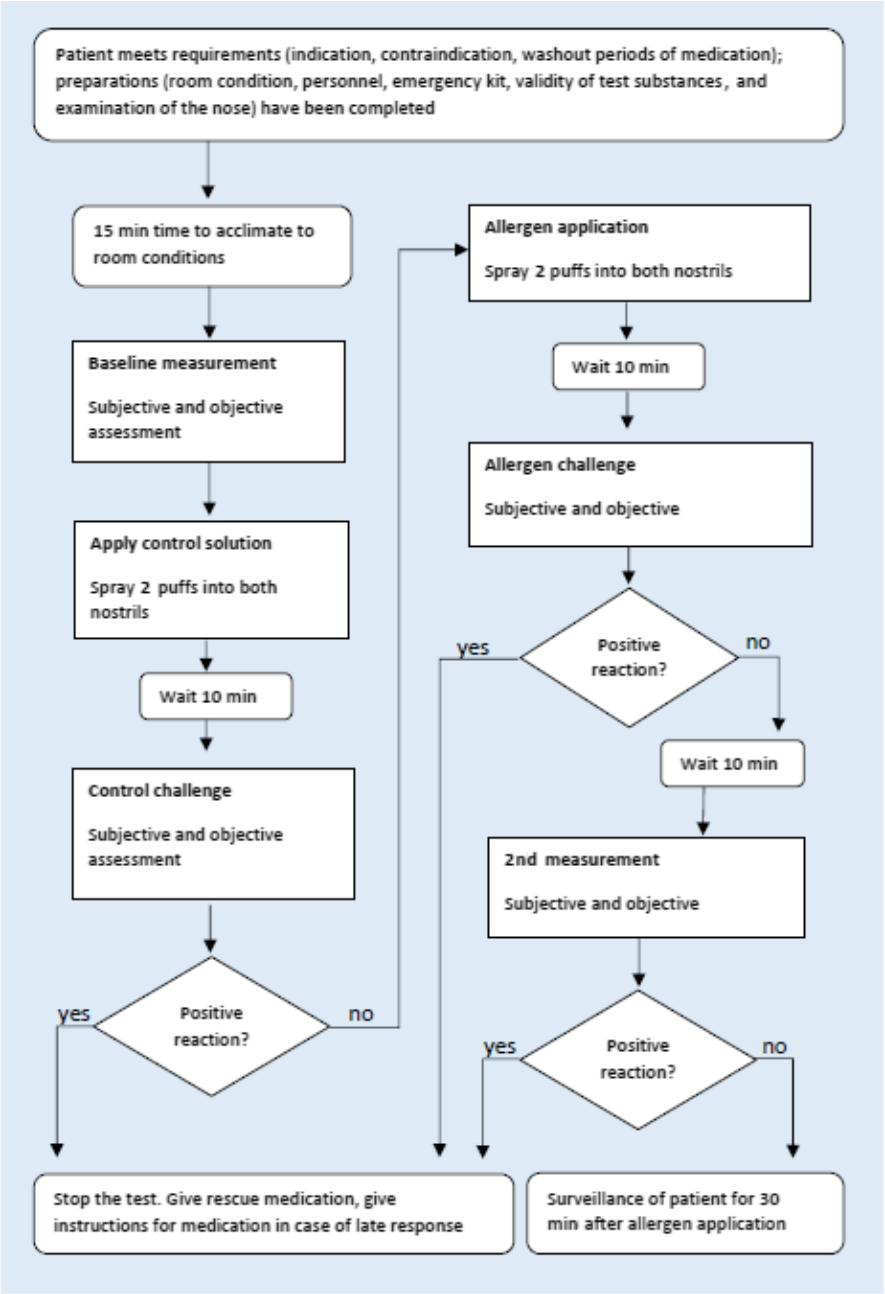

FIGURE 3 Schedule for nasal allergen challenges

3.6.2 | False-negative results

False-negative results can occur under:

- Exercise
- Nasal polyposis[47]
- Washout periods for medication received no consideration
- Lack of adaptation to room climate
- Wrong or expired test substances
- Faulty delivery of test solution
- Too low allergen concentration of relevant allergens (extrapolation from skin prick test agents)[29]
- Pronounced nasal obstruction at the start of the test

4 | CONCLUSION

Presently, the lack of a gapless and generally accepted guideline of NAC leads to different clinical interpretations. Therefore, this position paper, as proposed by the EAACI Standardization of NAC task force group of 32 members, has systematically reviewed all relevant clinical aspects of NAC and marked their potential advantages, as well as their respective drawbacks. Furthermore, specific recommendations on unmet needs were given on the basis of existing guidelines, a body of evidence, and the consensus of the task force members.

The task force suggests the use of standardized test solutions, to spray 2 puffs (0.1 mL per nostril) bilaterally and to evaluate clinical results of the challenge both subjectively and objectively.

Despite the co-existence of several equally validated methods to conduct NAC, it was the aim of this task force to provide a standardized, more user-friendly protocol of NAC for daily, clinical practice.

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CONFLICTS OF INTEREST

All authors have no conflicts of interest, except: RM Prof. Mösges is the chairman of the International Standardization Committee on Objective Assessment of the Nasal Airway (ISCOANA). OP Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from Novartis Pharma, personal fees from MEDA Pharma, grants and personal fees from Anergis S.A., personal fees from Sanofi US Services, personal fees from Mobile Chamber Experts (a GA^{2}LEN Partner), personal fees from Pohl-Boskamp, personal fees from Indoor Biotechnologies, outside the submitted work. MW Dr. Wagenmann reports personal fees from ALK-Abelló, grants from Allakos, grants and personal fees from Allergopharma, grants from Allergy Therapeutics, grants and personal fees from AstraZeneca, personal fees from Bencard, personal fees from Bionorica, grants from Biotech Tools, grants from GlaxoSmithKline, grants and personal fees from HAL Allergie, personal fees from MEDA Pharma, grants from Otonomy, personal fees from Stallergenes, grants from Strekin, outside the submitted work; JM Dr. MULLOL reports personal fees from SANOFI, grants and personal fees from MEDA Pharma, grants and personal fees from URIACH Group, personal fees from ALK-Abelló A/S, personal fees from Menarini Group, personal fees from MSD, personal fees from GlaxoSmithKline, personal fees from Novartis, personal fees from UCB Pharma, personal fees from GENENTECH, outside the submitted work. LK Dr. Klimek reports grants and personal fees from ALK Abelló, Denmark, personal fees from MEDA, Sweden, grants and personal fees from Novartis, Switzerland, grants and personal fees from Allergopharma, Germany, grants and personal fees from Bionorica, Germany, personal fees from Boehringer Ingelheim, Germany, grants and personal fees from GSK, Great Britain, grants and personal fees from Lofarma, Italy, grants from Biomay, Austria, grants from HAL, Netherlands, grants from LETI, Spain, grants from Roxall, Germany, grants from Bencard, Great Britain, outside the submitted work; SRD Dr. Durham reports grants and personal fees from ALK, grants from GSK, personal fees from Biomay, personal fees from Regeneron, personal fees from Boehringer Ingelheim, personal fees from UCB, personal fees and nonfinancial support from Allergy Therapeutic, personal fees from Anergis, outside the submitted work.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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