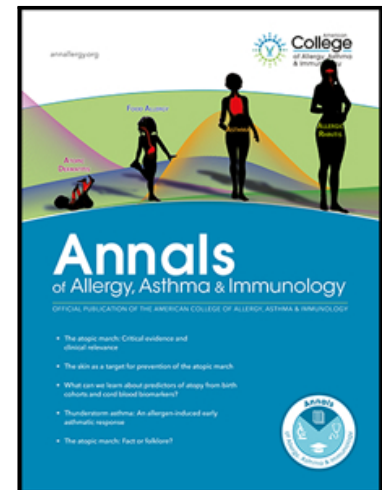


Comparing the NAC and EEU Models of Allergic Rhinitis

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Title: Comparing the NAC and EEU Models of Allergic Rhinitis

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Abbreviations:

Allergic rhinitis – AR

Allergen immunotherapy – AIT

Environmental Exposure Unit – EEU

House dust mite – HDM

Immunoglobulin-E – IgE

Nasal Allergen Challenge – NAC

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Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated hypersensitivity reaction triggered by allergen exposure that causes inflammation of the nasal cavity. Allergens can be seasonal, such as pollens and grasses, or perennial, including house dust mite (HDM) and animal dander. Historically, evaluations of novel AR therapies have been conducted using outpatient studies, whereby participants, having received a certain medication, go about their day-to-day routines during the expected pollen season. While clinically relevant, “real world” field studies are inherently limited by the heterogeneity of allergen exposure across different geographical locations and varying daily routines of participants. Field studies can also be associated with irregular compliance of medication and recording of daily symptom scores. Experimental models have been developed to counter these limitations, namely the Environmental Exposure Unit (EEU) and Nasal Allergen Challenge (NAC). The EEU is a controlled allergen challenge facility that allows for exposure of aerosolized whole allergen to a group of participants, whereas the NAC involves direct nasal delivery of a personalized dose of allergen extract. It is unclear how these models compare in replicating natural allergen exposure; hence this article recommends the preferential use of the NAC for modelling natural allergen exposure, especially of seasonal allergens, and studying AR pathophysiology and therapies.

NAC protocols, in which participants may receive a single or cumulative dose of allergen extract, typically begin with a control challenge excluding allergen to assess hyperresponsiveness to the diluent. If negative, participants will either receive a single preset dose of allergen or undergo NACs of increasing dose concentrations until a certain threshold of symptoms is reached. NACs permit personalized doses to be assessed, unlike the EEU, which aims to achieve a homogenous distribution of allergen, though it cannot guarantee equal allergen exposure of each participant. While the physical application of allergen into the nasal cavity may provoke some irritation, the effect is accounted for by including healthy control

subjects. Moreover, it also allows for investigations of allergic responses in specific regions of the nasal cavity.

EEUs and NACs both evaluate clinical symptom responses to allergen exposure differently. In EEUs, participants are exposed for a longer duration of time (3-8 hours), reflective of natural exposures to year-round perennial allergens. The NAC's direct and acute administration method mirrors seasonal environmental allergen exposure, sporadic and cumulative. While protocols vary, challenges are generally performed in both nasal airways to replicate inhalation of allergen. Tenn et al. showed that the NAC protocol, developed by the Allergen Rhinitis–Clinical Investigator Collaborative, produced AR symptoms comparable in severity to those induced in the EEU, though the pattern of symptoms induced by each model differed, potentially due to nasal distribution of allergen likely not reflective of natural occurrence regardless of NAC delivery method.¹ Similarly, Larson et al. found a lack of correlation between clinical data collected from the NAC and EEU protocols, supporting the notion that these two models cannot be used interchangeably.² While the EEU presents the advantage of controlling for temperature, humidity, and allergen concentration, among other variables, NACs with seasonal allergens are often completed out-of-season to ensure that natural environmental exposures do not present as confounding factors.

The NAC is more versatile and cost-effective. EEUs are specially designed facilities with limited availability that requires trained staff to manage the facility and large participant groups. NACs, on the other hand, require minimal specialized equipment and can notably be used for first-in-human studies, translating *in vitro* findings to human participants.³ This promotes innovation and exploration, especially with AR pharmacologic interventions for the treatment of persistent moderate-severe disease. As allergen immunotherapy (AIT) is the only disease-modifying option for AR, new formulations continue to be evaluated. NACs provide a suitable model for assessing long-term outcomes of AIT at repeated intervals with minimal costs and resources. An important consideration when investigating seasonal AR is the “priming effect” –

the phenomenon that repeated allergen exposure results in increased nasal hypersensitivity. EEU protocols sometimes take advantage of this effect by including a priming visit prior to the actual challenge to promote adequate, measurable symptomatic responses. Priming can also be considered with NACs, either achieved through repeated exposures or minimized by providing sufficient time between challenges for the nasal mucosa to return to its baseline state.⁴ This phenomenon remains understudied, though arguably, the NAC allows for greater flexibility for such investigations.

Safety is a critical consideration in clinical studies. While both EEU and NAC models have measures to ensure participant safety, efficacy and side effects of different medication dosages can be more easily assessed using the NAC due to the individualized nature of the protocol. Considering the current global pandemic, the NAC is a safer and more advantageous option than the EEU model, allowing for research continuation despite the conditions. With updated standard operating procedures to ensure proper safety measures, NAC participants can be isolated in a room for the duration of their challenge and be dealt with on a one-to-one basis by a single staff member donned in personal protective equipment. Any sneezing that occurs is confined within the room, without risk of exposing other participants. Once they have completed their NAC visit, the room can be thoroughly cleaned. In contrast, the EEU inherently involves a large group of participants in an enclosed space for an extended period during allergen exposure, undoubtedly providing much higher risks to all involved.

While neither the EEU nor NAC are perfect, here we present that the NAC is more advantageous and versatile and a better model of seasonal AR. Despite efforts, standardization remains a shortcoming for both models; however, given that NACs require less specialized equipment, it is likely for it to more easily be standardized to allow for bigger, multicenter studies.⁵ More data is needed to comparatively evaluate the use of field studies, EEUs, and NACs. “Hybrid studies” that integrate field studies with a controlled model are sparse in the current literature, though may provide novel insights. Nonetheless, given the current

circumstances, we propose the preferential use of the NAC for natural allergen exposure in the study of AR.

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Figure 1. Overview of the Nasal Allergen Challenge Model. Various protocols for the Nasal Allergen Challenge (NAC) model exist but most include a screening visit, where assessment of participant eligibility and a dosing challenge are completed, and an NAC visit, where an allergen extract is administered in an individualized dose. Depending on the study design, a diverse array of data can be collected to study AR manifestations.

THE NASAL ALLERGEN CHALLENGE

METHODS

Inclusion and Exclusion Criteria*:

- ✓ History of AR symptoms to inhaled allergen
- ✓ Positive skin prick test (≥ 3 mm wheal)
- ✗ Nasal structural abnormalities or polyps
- ✗ Positive history of HIV, TB, HBV, or HCV

* criteria may vary depending on study

Study Design:

Screening Visit	NAC Visit
- Assessment of eligibility	- Allergen challenge
- Qualifying allergen challenge	- Sample and data collection

Typical Composition:

- Allergen extract
- Saline

The concentration of allergen used is often the single Qualifying Dose or a Cumulative Dose of all concentrations evaluated during screening.

DATA COLLECTION

Symptomatic

Total Nasal Symptom Score; Peak Nasal Inspiratory Flow, etc

Biological

Serum cytokines; nasal cell counts; serum specific IgE, etc

Genetic

Serum cytokines; nasal cell counts, etc

Omics

Nasal microbiome; metabolomic analyses, etc.

