

CME Review

Environmental exposure unit: a sensitive, specific, and reproducible methodology for allergen challenge

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Learning Objectives:

At the conclusion of this activity, participants should be able to:

- Describe the Environmental Exposure Unit (EEU) methodology for controlled allergen challenge
- Discuss the technical aspects, study designs, and controlled variables in EEU studies that allow for the effective determination of onset of action and clinical efficacy of new anti-allergic treatments

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Allergic Rhinitis

Allergic rhinitis is a symptomatic nasal disorder involving IgE-mediated inflammation and hyperactive nasal mucosa, resulting in symptoms of rhinorrhea, sneezing, nasal pruritus, congestion, and aggravation of comorbid asthma.¹ The prevalence of allergic rhinitis is increasing and it currently affects approximately 10% to 25% of the population worldwide.¹ Although this disorder is often dismissed as a minor discomfort, because it is non-life-threatening, it has significant socioeconomic impacts, because it affects the productivity, education, and quality of life of sufferers.^{2,3} Treatments for allergic rhinitis include antihistamines, leukotriene modifiers, corticosteroids, cromolyns, and immunotherapy.⁴ Because a range of treatments is available, it is important that physicians have adequate information regarding their different pharmacologic properties, such as onset of action, so they can prescribe the most appropriate agent for their patients. Environmental exposure units (EEUs) play an important role in establishing the onset and duration of action and supporting the efficacy of new and established treatments.

Brief Historical Context of EEU Models

The EEU at Kingston General Hospital (Kingston, Ontario, Canada) was originally developed in 1981 by Dr James H. Day in the Division of Allergy, in collaboration with Professor Reginald Clark, Department of Chemical Engineering, Queen's University. The original unit was established to evaluate the physiologic effects of formaldehyde off-gasses and particulates associated with urea formaldehyde foam insulation, an insulation material that was widely used until the negative health effects on building occupants became clear.^{5,6} The EEU continued to be used in that capacity until 1987, when the increasing prevalence of allergic rhinitis and the necessity for effective treatments drove the adaptation of its specially engineered particulate distribution technology for allergy research. The goal of the EEU is to "bring the outdoors indoors,"⁷ but in a highly controlled way, effectively replicating the study conditions of an outdoor "park" study^{8,9} and removing many of the confounding variables that affect the results. The design of the EEU allows for allergen specificity, control over antigen exposure levels, temperature, and air quality, and an accurate way of tracking self-reported and physician-observed symptoms for determining response to medication.

Four years after the development of the EEU for urea formaldehyde foam insulation testing, one of the earliest documented allergen challenge environments was created in the United Kingdom and used to expose allergic participants, one at a time, to grass pollen levels ranging from 2,000 to 50,000 grains/m³.¹⁰ Although this system was successful in eliciting symptoms similar to those seen with natural pollen exposure, the investigator questioned the high pollen concentrations required to generate a response and acknowledged the need for more accurate control of pollen levels.¹⁰ The first multi-participant allergen challenge facility was the Vienna Challenge Chamber (VCC; Vienna, Austria), described by Horak and Jäger,¹¹ an enclosure inside which up to 9 people could originally be exposed, and up to 14 after subsequent rebuilding.^{4,11} As exposure units gained momentum by proving to be valuable tools in studying allergic diseases, interest developed in systems that were easy to establish using standard equipment.¹² Rønborg et al.¹² constructed such an exposure facility in Copenhagen, Denmark, and validated it for use with house dust mite allergen. Although admittedly an interesting model that could be adapted to any room, concerns such as the dependence on participant activity for air mixing and the fact that air sampling results are not available for ongoing adjustment of exposure levels are obvious drawbacks that may result in inconsistent exposures.¹² After the development and publication of the successful use of

the EEU in Kingston as a clinically relevant model of allergic rhinitis, similar facilities were developed independently in other locations across North America. In sequential order of publication, the Atlanta Exposure Unit^{13–15} (Atlanta, Georgia) and the Environmental Exposure Chamber^{16,17} (Mississauga, Ontario, Canada) have been used in several clinical trials to evaluate various antiallergic therapies. More recently validated and in use for clinical trials are the Biogenics Research Chamber^{18,19} (San Antonio, Texas) and the BioCube²⁰ (Andover, Massachusetts).

In the late 1990s, 2 exposure systems using live cats for antigen delivery of Fel d 1 were developed, 1 in Southampton, United Kingdom,²¹ the other at John's Hopkins University (Baltimore, Maryland).^{22,23} These "cat room" studies use the premise of a closed environment containing multiple cats whose presence induces allergic symptoms in cat-sensitive participants. The difficulty with this type of exposure unit is the extreme variability in antigen levels throughout exposure, which in some studies have ranged from 35 to 37,525 ng/m³ of Fel d 1.²² Thus, several EEU models have been developed, which use different clinically relevant allergens. All these models have been validated to induce symptoms in allergic participants, with varying levels of control over allergen levels, and each with its own unique advantages and drawbacks.

Technical Aspects of the EEU

The EEU, located in Kingston General Hospital, allows for the reliable exposure of up to 140 participants to predetermined levels of allergen, which remain consistent regardless of outside weather conditions, to determine the efficacy and onset of action of new therapies for allergic rhinitis.²⁴ The EEU setup, including location of chairs, feeder, fans, and Rotorod sampling equipment (Sampling Technologies Inc, Minnetonka, Minnesota), is illustrated in [Figure 1](#). A custom-engineered computer and laser-aided system disperse pollen at a single point of delivery ([Fig 1](#)). The pollen is propelled, by selectively placed groups of directional fans, over the participant seating area. For EEU studies, pollen is typically sourced from Greer Laboratories (Lenoir, North Carolina). Before use, pollen is independently tested for fungal and bacterial contamination (Paracel Laboratories, Ottawa, Ontario, Canada). Any concentration of pollen from 200 to 10,000 grains/m³ can be achieved for as long as required, limited only by participant tolerance, and studies have been carried out for up to 14 continuous hours of exposure.^{24,25} Typically, ragweed and grass studies in the EEU target 3,500 grains/m³, which is consistent with peak seasonal levels, and can be delivered on consecutive days with an average variability of only 5% to 9%.^{24,26} Rotorod impact samplers rotate sampling rods at 2,400 rpm, sampling 47.3 L of air per minute by collecting pollen grains on their greased surfaces, which can be microscopically counted. Samples are taken for 30 seconds at 30-minute intervals, which correspond to the participant symptom scoring times. The 7 Rotorod samplers are distributed throughout the participant seating area and pollen levels are monitored and recorded throughout each clinical study period. Pollen levels in the EEU have been shown to be consistent throughout the participant seating area and over time during different study periods.^{24,27} The ventilation system uses filtered outdoor air, with temperature (18°C to 22°C) and humidity (40% to 60%) control, and the CO₂-laden air is exhausted directly to the outdoors. The room is kept under slightly negative pressure to minimize pollen loss to the rest of the hospital. Throughout the study, participants record their symptoms on diary cards, which are scanned into a locked database, providing real-time data in graphic format within 20 minutes of each data collection period. Thus, the technical aspects of the EEU, including the ability to deliver measured levels of pollen over extended times and to accurately record participant symptoms, allow this model to reliably evaluate specific attributes of antiallergic medications.

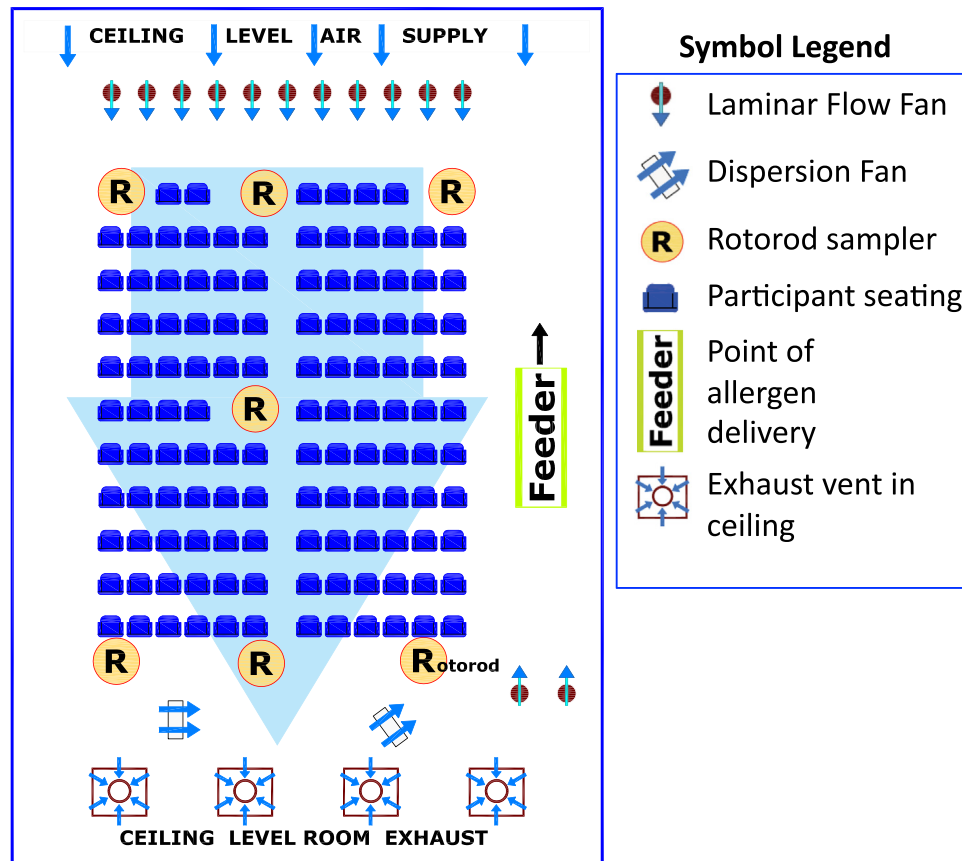


Figure 1. Map of the Kingston environmental exposure unit. This diagram shows the placement of the pollen distribution system, point of allergen delivery, directional fans, Rotorod pollen samplers, ventilation, and participant seating.

The duration of allergen exposure tends to be 3 to 8 hours, depending on the nature of the treatment and whether the study seeks to determine the onset of action or duration of action. Some studies have involved 14 hours of pollen exposure, when the objective was to determine the onset of action of a nasal corticosteroid.^{25,28}

Symptom Development in EEU Models and Reproducibility of Findings

The priming effect is defined as an increase in reactivity of the nasal membrane after repeated exposure to allergen.²⁹ In EEU, the purpose of priming is to increase sensitivity to a specific allergen, inducing mucosal inflammation and facilitating the development of adequate symptoms for participant inclusion. The rate and degree of symptom development vary among individuals. Factors that have been associated with the rate and degree of symptom development include positive skin prick test results to dust mite, dog, or grass, self-reported exposure to dog or cat, and rhinitis-related quality of life.³⁰ The inclusion of the priming phase in EEU studies has been shown to standardize predose symptoms and greatly decrease symptom variability in the treatment phase or during baseline assessments.²⁷

Ensuring the safety of participants in EEU trials is paramount. Exposure to allergen in the EEU has been proved to be safe and well tolerated.⁴ A serious allergic reaction requiring resuscitation has never occurred in the longer than 25-year history of the EEU. However, because a serious allergic reaction always remains a possibility during these types of studies, the unit maintains emergency response procedures for the management of anaphylaxis, in accordance with established guidelines.^{31–33} A potential

safety advantage of EEU studies is the location of the unit directly within an acute tertiary care hospital, allowing for seamless transfer of care of a participant to the emergency department if necessary (with accompaniment during transfer and appropriate follow-up by a study doctor). Rescue medications (eg, antihistamines) to help relieve symptoms of allergic rhinitis induced in the EEU are not typically provided to participants after an allergen exposure, depending on the constraints of the study protocol. However, after the completion of a trial, participants are typically free to begin using antiallergic medications as recommended by their health care providers. The authors previously showed that participants in EEU research trials experience temporary (average 2.5 weeks) decreases in their quality of life in parameters specific to their rhinoconjunctivitis.³⁴ Of note, participants' quality of life before entering an EEU study has been shown to affect their response to placebo.³⁵ Knowledge of these effects can assist in designing a trial that will yield optimal results. Although participating in an EEU study does negatively affect participants' quality of life for a short time, participating in phase 3 natural season trials, which may last the entire duration of the pollen season, also has the potential to affect quality of life and, depending on the study design, may actually do so for a longer period.

Reproducibility of clinical findings between studies is an important issue in allergic rhinitis research. If conditions are tightly controlled in an EEU, repetition of the same protocol on separate occasions should yield the same results. Indeed, the VCC and the Kingston EEU have shown this to hold true. Two studies performed in the VCC investigated the effect of desloratadine on nasal congestion and showed similar results.^{36,37} In the Kingston EEU, a study examining the effects of cetirizine or loratadine vs placebo was conducted in 1995 and repeated in 1999.^{38,39} These studies

yielded almost identical comparative efficacy results despite being conducted years apart. Recently, using the Biogenics Research Chamber, Jacobs et al⁴⁰ reported a high degree of concordance between allergic symptoms induced on exposure to pollen in an EEU and those experienced during the natural season.⁴⁰ Thus, placebo and medication responses are highly reproducible across EEU studies, and symptom development within participants correlates with that during natural exposure.

Other Allergic Rhinitis Study Models

Three major classes of allergic rhinitis studies that have been recognized by the US Food and Drug Administration and the European Medicines Agency are standard phase 3 efficacy, park setting, and EEU.^{41,42} The authors have discussed the brief history, technical aspects, and the induction of allergic rhinitis symptoms in EEU and now briefly discuss how they compare with other common experimental models.

A standard phase 3 efficacy study uses the participant's natural environment as a vehicle for allergen delivery and relies on participants to comply with the treatment schedule and record their symptoms.^{27,43} Studies are normally randomized, double blinded, and placebo controlled. Standard phase 3 studies have the advantage of enrolling large numbers of participants at multiple sites and observing long-term response to medication. However, they are limited by pollen production during the study period, weather conditions, differential pollen exposure within the study population, potential concurrent exposure to multiple allergens, and reliability of participant dosing and reporting. Common study designs are parallel-group designs, comparing at least 1 treatment arm with placebo, and crossover designs. Owing to the lack of participant matching, parallel-group studies are typically multicenter, because they require a large number of participants to achieve statistical power.⁴ Crossover designs assume that allergic rhinitis symptoms are stable over time, assume that washout periods are sufficient, may not account adequately for the priming effect, and are limited by the length of the pollen season.⁴

Park studies have been conducted since the late 1970s⁴⁴ and use an outdoor setting during the pollen season to expose participants to environmental allergens in a randomized, double-blinded, and placebo-controlled manner. Studies in park settings control certain variables, such as similar pollen exposure levels between participants on a given day, precise timing of study drug administration, accurate timing of symptom reporting, and recorded pollen counts. There have been several well-designed studies used to test anti-allergic medications, and the park model can be used to determine important pharmacodynamic parameters, such as onset of action.^{8,9} However, park studies remain season and weather dependent. Participants enter the study with pre-existing symptoms, which may be due to perennial and seasonal allergens, and exposures before and during the park study may vary across multiple study sites.⁴ There can be interindividual differences in exposure levels across study sites, across study days, and even within the same exposure group, owing to the largely unknown location of mixed pollen sources in the park and uncontrollable wind currents. Pollen counting during park studies, whether carried out onsite or estimated from counts made at a central location, can be a challenge owing to the variety of species of pollen present in the outdoor air and pollen fragmentation. Concurrent exposure of participants to outdoor air pollution, including gasses, particulate matter, and volatile chemicals, may affect symptom development, and pollution may be adsorbed onto outdoor pollen grains, affecting antigenicity.⁴⁵

Thus, standard phase 3 trials play an important role in establishing the efficacy of new treatments for allergic rhinitis. Although they have many limitations, these can generally be overcome by

enrolling large samples, and to date they remain the only model that is considered from a regulatory standpoint to represent "real life." The park model controls for several additional factors and has the capacity to determine important treatment characteristics and provide data supporting efficacy. However, there are practical difficulties that make it difficult for park studies to prove repeatable, because pollen seasons and weather conditions can never be replicated. Thus, EEU studies evolved to control additional factors that are reproducible day to day and season to season. These include allergen specificity, controlled and recorded pollen levels throughout the room and throughout the exposure period, and environmental factors such as air quality, humidity, and temperature. The results of these trials are directly applicable to real-life applications in clinical practice because the practitioner can be assured response to treatment is not artificially induced by a lack of allergen exposure.

Clinical Trial Results

Antihistamines and Antileukotrienes

Environmental exposure units have been used extensively to compare the efficacy and onset of action of various antihistamines. The second-generation antihistamines terfenadine, astemizole, cetirizine, and loratadine and their ability to produce relief of allergic rhinitis symptoms were investigated in the Kingston EEU.⁴⁶ This study was able to rank the treatments of interest, with the conclusion that cetirizine and terfenadine continuously ranked higher in onset of action and efficacy, whereas loratadine and astemizole ranked lower.⁴⁶ This was followed by a study with larger participant numbers to specifically compare cetirizine, loratadine, and placebo.³⁹ This follow-up investigation confirmed that cetirizine significantly decreased total symptoms compared with loratadine and placebo, with an onset of action of 60 minutes.³⁹ Fexofenadine is the active metabolite of terfenadine, considered a third-generation antihistamine. One of the first published trials of its efficacy was conducted in the EEU.⁴⁷ Two different doses of fexofenadine (60 and 120 mg) were compared with placebo and provided clinically important relief of allergic rhinitis symptoms, with a median time to onset of 60 minutes.⁴⁷ The durations of effect of cetirizine and fexofenadine at specific time points were examined further in the EEU. One study reported that cetirizine produced a significantly greater decrease in total symptoms, runny nose, sneezing, itchy/watery eyes, and itchy nose/throat/palate compared with fexofenadine (180 mg) 5 to 12 hours after the dose.⁴⁸ Another study compared the 2 treatments on 2 consecutive days and found that cetirizine produced a 33% larger effect on symptom decrease compared with fexofenadine (180 mg) over the 21- to 24-hour interval, indicating a superior and longer duration of effect.⁴⁹

The EEU model has been used to directly compare H₁-receptor antagonists with antileukotrienes. The efficacies of levocetirizine (5 mg) and montelukast (10 mg) were compared in a randomized, double-blinded, placebo-controlled, parallel-group study in ragweed-sensitive participants exposed to ragweed pollen.^{50,51} Participants received levocetirizine, montelukast, or placebo orally once daily for 2 consecutive days during EEU ragweed exposures. The 2 active drugs significantly improved the major symptom complex compared with placebo.^{50,51} Levocetirizine was superior to montelukast during the 22.5 to 24 hours after the first dose and during the 4.5-hour period after the second administration of study drug.^{50,51} Participant-reported global satisfaction also was greater for levocetirizine compared with montelukast and placebo.^{50,51} Thus, EEU studies are useful for comparing drugs that target independent pathways that contribute to seasonal allergic rhinitis symptoms.

Useful information regarding combination therapies also can be ascertained using the EEU. Nasal congestion has been reported to

be one of the most bothersome symptoms of allergic rhinitis by patients and has been the most difficult to treat effectively. A study was carried out in the EEU to compare the efficacy of a single dose of loratadine/montelukast combination with phenylephrine and placebo during a 6-hour postdose exposure to ragweed.⁵² In this double-blinded, randomized, placebo-controlled, parallel-group study, loratadine/montelukast produced a greater decrease in congestion scores compared with phenylephrine and placebo.⁵² Loratadine/montelukast also was significantly superior to phenylephrine and placebo with respect to total symptoms, nasal symptoms, non-nasal symptoms, and peak nasal inspiratory flow.⁵² The onset of action of a combination antihistamine/leukotriene receptor antagonist nasal spray (loratadine 10 mg/montelukast 10 mg) was subsequently evaluated in detail in the EEU in a double-blinded, parallel-group study of ragweed-sensitive participants with allergic rhinitis.⁵³ This study reported an onset of action of 1 hour 15 minutes against total symptom scores, nasal congestion, and peak nasal inspiratory flow.⁵³

The importance of routes of administration has been examined in EEU studies. Recently, the Kingston EEU was used to evaluate azelastine nasal spray vs orally administered cetirizine, loratadine, or placebo.⁵⁴ Azelastine nasal spray significantly decreased nasal symptoms compared with placebo and exhibited a 15-minute onset of action compared with 60- and 75-minute onsets of action for cetirizine and loratadine, respectively.⁵⁴ Because onset of action is an important characteristic from a patient's perspective, EEU studies make important contributions toward understanding the pharmacologic effects of medications, which are relevant to clinicians who prescribe these medications to their patients.

Nasal Corticosteroids

Environmental exposure unit studies are ideal to work hand in hand with traditional outpatient studies. The authors' group partnered with the 194-079 Study Group to compare mometasone furoate with fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis.⁵⁵ This 3-month, multicenter, double-blinded, double-dummy, placebo-controlled, parallel-group study showed that the 2 active treatments provided significant relief of symptoms compared with placebo.⁵⁵ However, mometasone furoate was significantly superior to fluticasone propionate for physician-evaluated decrease of nasal discharge and congestion at the mid-study and end-study time points.⁵⁵ The first evaluation of a nasal corticosteroid in the EEU investigated the onset of action of triamcinolone acetonide.⁵⁶ Participants received study medication for 7 days under supervision in the morning and were challenged with ragweed pollen in the evening in the EEU. This study surprisingly showed a 10-hour clinically relevant onset of action, defined as a 25% decrease in symptom scores from baseline.⁵⁶ In addition, the proportion of participants with less nasal congestion after 1 day of treatment was significantly larger in the triamcinolone acetonide group.⁵⁶ It was previously thought that nasal corticosteroids would require several days for the onset of action to occur. In response to this finding, the onset of action of budesonide nasal spray was evaluated in the EEU.²⁵ It was determined that the onset of action was 7 hours with respect to total nasal symptoms, but evidence of efficacy was shown at 3 hours by a significant improvement in peak nasal inspiratory flow.²⁵

Immunotherapy

The efficacy of immunotherapy was examined using controlled pollen challenge in the EEU.⁵⁷ Two years of immunotherapy was found to significantly decrease symptoms, which reached significance compared with nontreated controls at 45 minutes.⁵⁷ The VCC also was used recently to evaluate a new 5-grass-pollen sublingual immunotherapy tablet.⁵⁸ An allergen challenge with grass pollen

was carried out at baseline, 1 week, and 1, 2, and 4 months of treatment. A significant effect of sublingual immunotherapy on symptoms during challenge was shown at 1 month and maintained to 4 months.⁵⁸

Conclusions

The EEU model is a unique system that overcomes certain challenges evident in standard phase 3 efficacy trials and park studies by controlling additional study variables. EEU studies have been used to prime allergic responses in allergic participants, show the efficacy of various antiallergic therapies, and evaluate the onset and duration of action of new therapies. These systems provide important information about the pharmacodynamic properties and support the efficacy of antiallergic treatments.

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